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VOLUME 38 AUGUST, 1926 NUMBER 2

CLINICAL PHYSIOLOGY OF THE STOMACH

SIMULTANEOUS QUANTITATIVE OBSERVATIONS ON GASTRIC SECRETORY VOLUME, ACIDITY AND MOTILITY *

ARTHUR L. BLOOMFIELD, M.D.
AND
CHESTER S. KEEFER, M.D.
BALTIMORE

In a previous article [1] we described a method by which it was possible to estimate the amount of gastric juice secreted and discharged from the stomach in successive ten minute periods following the introduction of a standard stimulus (alcohol). We have now examined a considerable number of people with and without gastric symptoms and the present article deals with some of the data derived from these studies.

THE VOLUME OF GASTRIC JUICE SECRETED BY PEOPLE WITHOUT DIGESTIVE SYMPTOMS

In setting biologic standards it is usually customary to select persons that most nearly approximate normal, and in studying normal gastric function it might at first seem best to study a group of healthy young adults without present symptoms, and with the minimum of past diseases. However, in dealing with patients with digestive symptoms when a diagnostic problem exists, it would be misleading to compare with a supernormal standard, and what one desires to know is the range of variation in people of various ages and of various physical fitness who have no evidence of gastric disease. For this reason the present material comprises a miscellaneous group of people—all ward patients—none of whom, however, had any history or signs of digestive disturbance and all of whom were afebrile, without severe anemia, ambulatory, and in fairly good general condition. A good many members of the group were to all intents and purposes normal people. Thirty patients were studied and the main facts that have been brought out are summarized in the accompanying table.

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* From the biological division of the medical clinic, Johns Hopkins University Medical Department and Hospital.

1. Bloomfield, A. L., and Keefer, C. S.: A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man, Arch. Int. Med., to be published.

Summary of Gastric Examination of Thirty People

Case	Diagnosis	Age	Sex*	Volume of Gastric Secretion in Ten Minute Periods						Highest Acidity Reached During Test; Titration with N/10 NaOH	Largest Volume of Stomach Contents During Test	Emptying Time of Stomach, Minutes	Average Volume of Ten Minute Secretion, Cc.	
				Period 1	Period 2	Period 3	Period 4	Period 5	Period 6					
54	Bradycardia	50	♂	24.5	20	11	9.5	7	....	0	64	65	12.5	
60	Normal	19	♂	36	13	21	....	....	....	93	60	55	23	
62	Normal	14	♂	...	45	42	42	37	....	55	150	90+	41.5	
80	Normal	49	♂	24.5	16	13	13	11.5	9	43	67	75	14.5	Convalescent from bronchitis; temperature normal for two weeks
82	Normal	45	♂	26.5	31.5	....	....	....	....	95	62	35	29	Entered hospital for sciatica
84	Normal	15	♀	22	10	10	18.5	16.5	6.5	73	62	65	14	
86	Normal	15	♀	19	14.5	19.5	15	8.5	....	54	52	75	15.5	
94	Arteriosclerosis; slight hypertension	51	♂	10	12	13	6	5.5	....	34	48	50	9.5	
96	Convalescent acute nephritis	42	♂	16.5	....	....	....	....	....	32	176	20	..	
88	Normal	25	♀	34	18	14	....	....	....	42	56	40	22	
110	Psychoneurosis	47	♂♀	24.5	14	8	....	....	....	118	36	30	19	
116	Normal	49	♂	30.5	....	....	....	....	....	35	40	20	..	Convalescent from bronchopneumonia
124	Normal	23	♂	35	24	16	....	....	....	86	60	40	25	
130	Syphilis; periostitis	14	♂	30	27	15	....	....	....	75	55	50	24	Patient clinically well at time of test
132	Normal	23	♂	35.5	37.5	35	....	....	....	76	60	50	36	
136	Normal	68	♂♀	21	13	9	11	....	....	71	60	60+	13.5	
138	Normal	34	♂♀	29	20.5	....	....	....	....	0	32	30	25	
158	Bradycardia	56	♂♀	70	66	56	....	....	....	74	125	70+	64	
168	Old stricture of rectum	29	♂♀	13	11	9	6	....	....	0	50	40	10	
176	Hypertension (moderate)	40	♂♀	27.5	24	18	12	11.5	8	98	64	80	17	No symptoms at time of test
182	Normal	22	♂♀	23.5	17.5	34.5	32.5	16.5	20.5	20	80	80	24	
188	Gonorrheal arthritis	19	♂♀	21	13	19	18	....	....	57	56	50	18	Well at time of test
196	Normal	28	♂♀	21	16	20	15	7	....	100	70	70+	16	
198	Normal	14	♂♀	27	40	15.5	29.5	17.5	....	69	64	70	26	
202	Old rheumatic endocarditis	31	♂♀	18	23	....	....	....	....	5	50	50	21	No symptoms
208	Hematuria, unexplained	17	♂♀	25	56	14	....	....	....	95	86	70+	32	
210	Myocardial insufficiency	40	♂♀	40	47	14.5	....	....	....	0	84	60+	35.5	No symptoms at time of test
222	Psychoneurosis	27	♂♀	23	25	....	....	....	....	15	44	30	24	
228	Angina pectoris	51	♂♀	23.5	16	....	....	....	....	0	52	30	20	
230	Dysthyroidism	50	♀	22	15.5	21	23.5	13.5	....	0	60	60+	19.5	

* In this table, ♂ indicates male; ♀, female.

Chart 1 shows graphically the maximum amount of juice secreted in a ten minute period. Each block represents a different case. It appears that twenty-two of the thirty people studied, or 73 per cent, secreted a maximum of from 20 to 40 cc. in ten minutes. Chart 2, constructed in a similar way, shows the average secretion of two or more ten minute periods. Here again in about 73 per cent of the cases the amount varied from 10 to 30 cc. In regard to the few persons who secreted the smallest and largest quantities of juice it may be said again

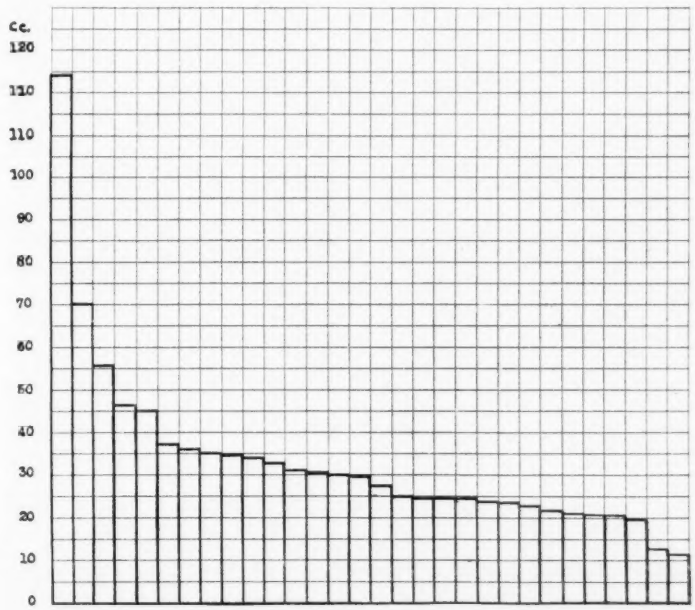

Chart 1.—Maximum volume of gastric juice secreted in ten minutes.

that they were without digestive symptoms or evidence of gastric disease, and were in no way distinguishable from the major portion of the group.

It appears, therefore, that from 10 to 30 cc. represents the usual average ten minute secretion but that in occasional individuals the amount may be larger or smaller.

THE DEGREE OF ACIDITY OF GASTRIC JUICE SECRETED BY PEOPLE WITHOUT DIGESTIVE SYMPTOMS

A great many observations dealing with the acidity of the gastric contents of normal people as determined by plain or fractional test meals

are on record, and the results are usually classified on the familiar basis of hyperacidity, normal acidity, subacidity and anacidity. In Chart 3 is shown the highest acidity (titration with phenolphthalein) of the pure gastric juice reached at any time during the examination of each patient. Each column represents a different person. The striking feature of the chart is the steady graduation from low acidities up to high ones. These observations, together with many others, not here included suggest that it is perhaps unwise to define any rigid standard of normal acidity as the variations are so wide. This point will be discussed further in connection with the diagnostic significance of the gastric secretion.

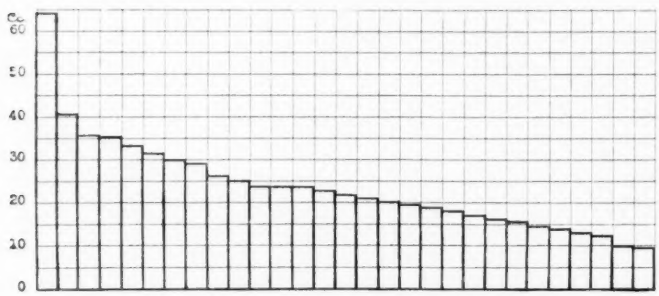

Chart 2.—Volume of gastric juice secreted in ten minutes (average of several ten minute periods).

THE RELATION OF THE DEGREE OF ACIDITY TO VOLUME OF GASTRIC JUICE SECRETED

At the beginning of these studies it was suspected that there might be some relationship between the degree of acidity of the gastric juice and the volume secreted. Chart 4, in which maximum secretion per ten minute period is plotted against maximum acidity, shows this not to be the case. With volumes of 25 cc., for example, acidities all the way from 0 to 120 were encountered. It may be seen, too, that the volumes secreted in the anacidity cases varied greatly. After all this is quite comprehensible when the complexity of the whole matter is considered and the various elements of the gastric secretion—mucus, acid and pepsin—which probably are not all produced by the same cells, are taken into account. It may be emphasized that these findings have nothing to do with the fact, which is well known and which we have confirmed, that the acidity may increase in the individual case as volume of secretion increases after stimulation.

GASTRIC MOTILITY IN PEOPLE WITHOUT DIGESTIVE SYMPTOMS

If one takes as a measure of gastric motility the amount of stomach contents which passes the pylorus in a unit of time, it immediately becomes apparent that the same quantity may be ejected under rather diverse conditions. If the pylorus is widely open much material may pass out with few contraction waves; on the other hand, with closure of the pylorus considerable gastric motor activity will be necessary to eject the same amount of material. Furthermore, the matter is complicated by the fact that as the stomach becomes empty secretion usually

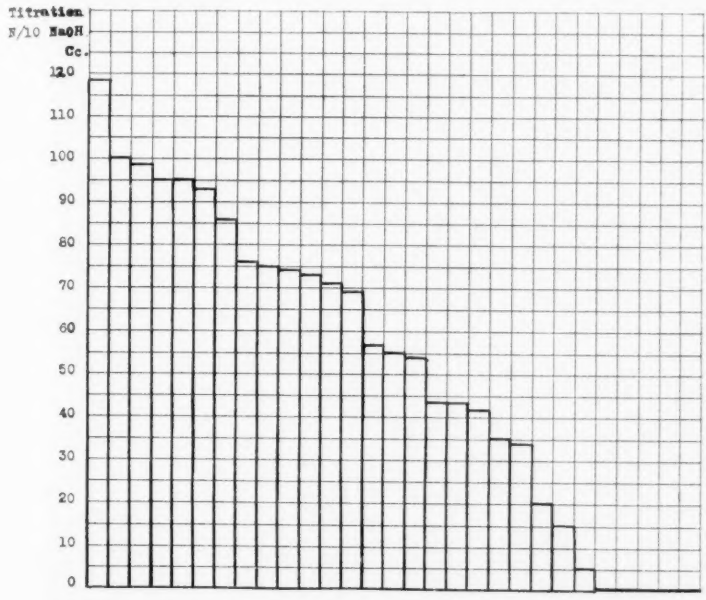

Chart 3.—Highest acidity reached in each case (titration with phenolphthalein).

diminishes; the very fact that the pylorus is closed tends to keep up secretion. It seems safer, therefore, to confine the present analysis of gastric motility to a few relatively simple facts.

In each observation a standard quantity of fluid was introduced through the tube into the fasting stomach and by complete aspiration at ten minute intervals it was possible to plot curves of the volume of gastric contents which at any moment consists of the fluid introduced plus the juice secreted less the quantity of material passed out of the stomach or absorbed through its walls. Two types of reaction were noted. In some cases there was an immediate decrease in the volume of

stomach contents. This decrease continued until the stomach had emptied itself with greater or less rapidity. In other observations there was an increase of volume lasting for a variable length of time and then a decrease. In practically every instance, however, the course of the curve was smooth, that is to say there were no rapid or repeated fluctuations from larger to smaller volumes. Several representative curves illustrating this point are shown in chart 5.

In chart 6 are shown the highest volumes of stomach contents reached during the tests. Each column represents a different case. It is seen at once that the response to an identical stimulus is very different

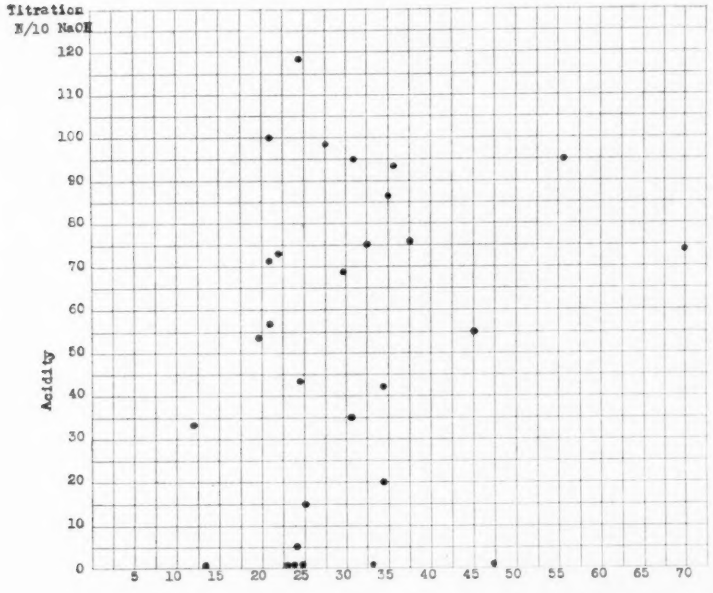

Chart 4.—Relation of volume of secretion to acidity in different people.

in different observations and two explanations suggest themselves. First, a very large secretion of gastric juice may as it were "flood" the stomach so that volume of contents rises; on the other hand, the volume whether large or small might be explained by the readiness with which fluid passes out of the stomach. That the second possibility is in the main correct is shown by a further consideration of chart 6. In the lower shaded part of each column is indicated the average volume of juice secreted in ten minutes. It is seen that there is no clear relation between this quantity and the total volume of stomach contents. Neither does the degree of acidity of the gastric juice seem to have any bearing on the

total contents of the stomach. The dots in chart 6 indicate the maximum titratable acidity in each case and it may be seen that similar volume relations follow in persons whose acidity may vary from 0 to 100. These observations may, we believe, be taken as evidence against the theory of acid control of the pylorus, a theory that has been questioned recently by various writers.

If we turn now to the question of gastric motility from the standpoint of the emptying time of the stomach the results of our observations

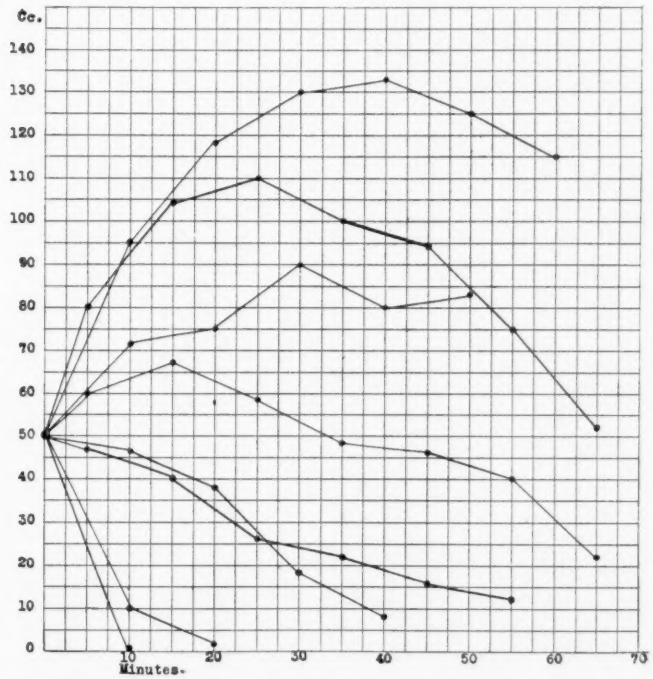

Chart 5.—Volume curves of stomach contents in various people (ten minute intervals after a standard meal of 50 cc. of 7 per cent alcohol solution).

are shown in chart 7. Each column represents the number of minutes that elapsed after the introduction of the standard 50 cc. meal until the stomach was empty (contents 10 cc. or less). It is seen that the emptying time under these conditions varied in different people from twenty to over ninety minutes. No correlation with volume of secretion (average for ten minute period—shaded column) or with acidity (dotted line) can be made out.

FINDINGS ON REPEATED EXAMINATIONS OF PEOPLE WITHOUT DIGESTIVE SYMPTOMS

In order to appreciate changes in gastric functions which result from disease and to evaluate properly the results of treatment, it is necessary to know the range of variation in the same person at various times. A good many observations on repeated tests of gastric acidity by the Ewald meal and the fractional meal are on record. In some instances considerable variation has been reported but the most recently

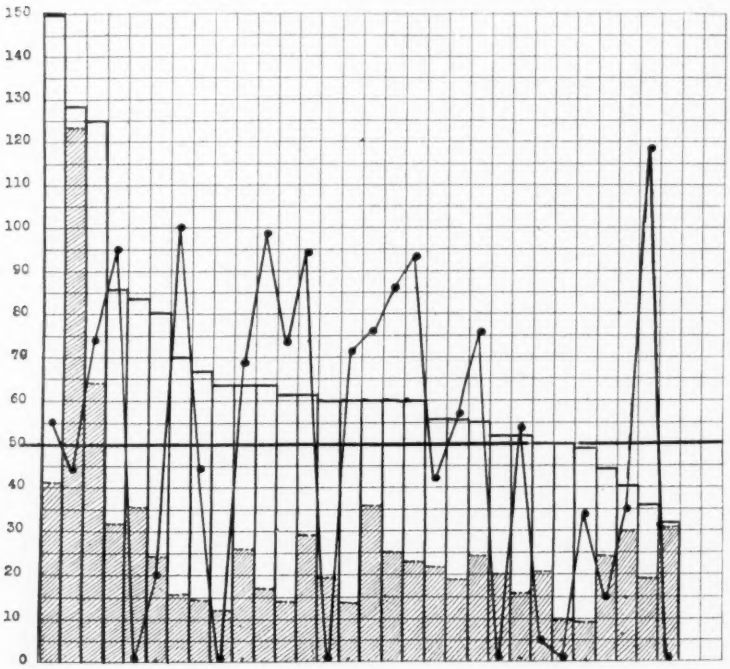

Chart 6.—Relation of highest volume of gastric contents (unshaded columns, cubic centimeters) to volume of gastric secretion (shaded columns, cubic centimeters) and acidity (dots titrable acidity).

and carefully controlled examinations seem to indicate that with the fractional meal the same general type of curve is fairly constant in the individual. The literature on this subject is reviewed by Bell and McAdam.[2]

In the present work the relations of acidity, volume of secretion and motility as found on repeated examinations are analyzed. In sixteen

2. Bell, J. R., and MacAdam, W.: Am. J. M. Sc. **167**:520 (April) 1924.

of our control group repeated examinations were made and in chart 8 are shown the results as regards the maximum titratable acidity which was reached. The dots in each vertical column refer to the acid values in one person, each dot indicating the result of a separate test. The second and third examinations were made after intervals of from one week to several months, but the highest values, regardless of whether they were obtained on the first or on a repeated examination, are charted in the upper curve. It is apparent that the acid values remain remarkably constant; in no instance was there a transition from low acidity to high acidity or vice versa. This is the more significant when it is recalled

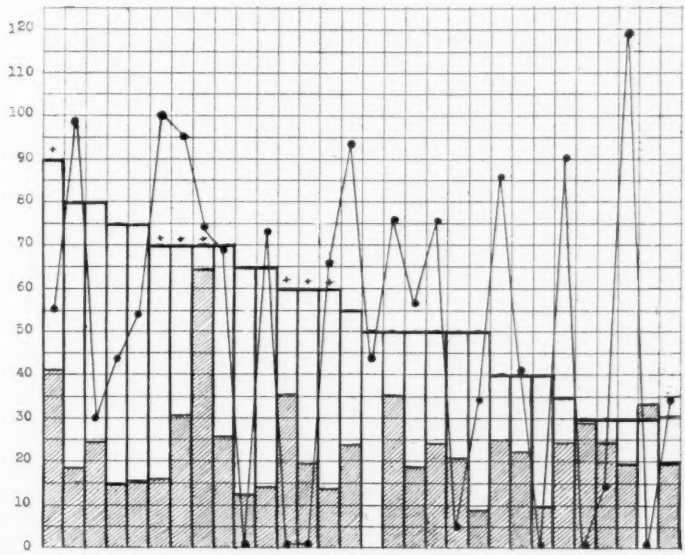

Chart 7.—Relation of emptying time of stomach (unshaded columns, minutes) to volume of secretion (shaded columns, cubic centimeters) and acidity (dots titration with tenth normal sodium hydroxide).

that these figures do not refer to acidity of juice as secreted but to the highest acidity attained by the mixed juice in the stomach during the examination, a value which obviously must vary with motility and volume. It would seem therefore, that under uniform conditions of examination a normal person secretes a gastric juice of *highly constant acidity*.

In chart 9 the findings as regards volume of gastric juice secreted on repeated examinations are shown. Each dot represents the number of cubic centimeters of secretion during ten minutes, the value being obtained from an average of the various ten minute periods of the

entire examination. The two dots in each vertical column indicate the results of two tests of the same person. The second test was done within from one week to three months after the first, but the highest value in each case is placed above the lower regardless of sequence of examination. It is seen that the volumes secreted by a particular person are remarkably uniform on successive examinations.

When we turn to the question of motility the findings are quite different. In chart 10 each group of vertical columns represents in cubic centimeters the highest volumes reached in the stomach during repeated tests of the same person. It is seen that in a good many cases

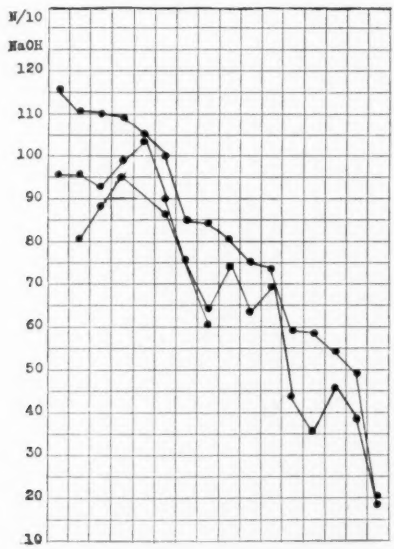

Chart 8.—Acidity of gastric juice on repeated examinations of same persons.

the results were quite variable. The dots indicate the emptying time in each test. Here even more variation is apparent as illustrated by the cases in which emptying times of ten and of seventy minutes were found on successive occasions.

COMMENT

In the charts we have presented the results of a simultaneous quantitative study of gastric secretion, acidity and motility following a standard stimulus in essentially normal people without digestive symptoms. Two distinct facts are brought out: (1) that the volume of secretion and the degree of acidity vary within considerable limits in different people but under the conditions of these experiments are practically constant

in the same person on repeated examinations, whereas (2) the motility is extremely variable. There was no relation, in the group between reaction of stomach contents and age, sex, condition, blood count and extra-abdominal disease, to mention only a few of the factors which it is alleged affects gastric acidity. *A priori* there is no reason to believe that all "normal" human beings do or should secrete a gastric juice of

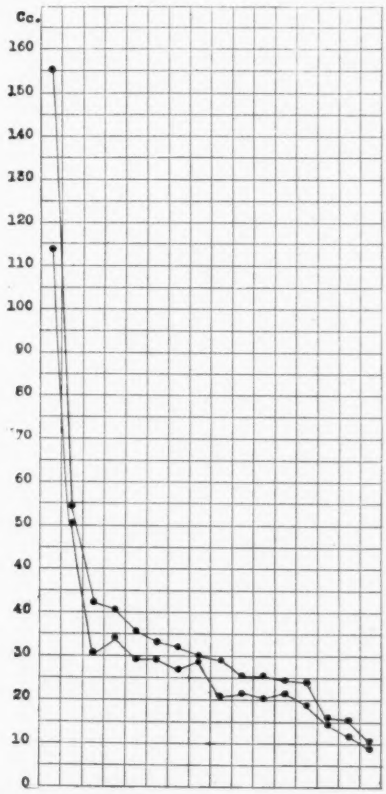

Chart 9.—Volume of gastric secretion on repeated examination of same persons.

uniform composition any more than that they all secrete the same volume and quality of sweat in response to the same stimulus. The demands from the standpoint of regulation of body constants are not at all to be compared with those obtaining in the case, for example, of blood reaction. For the given individual, however, the type of response to a constant gastric stimulus seems quite fixed as regards acidity and volume of secretion. What, if any, factors may alter this individual reaction are

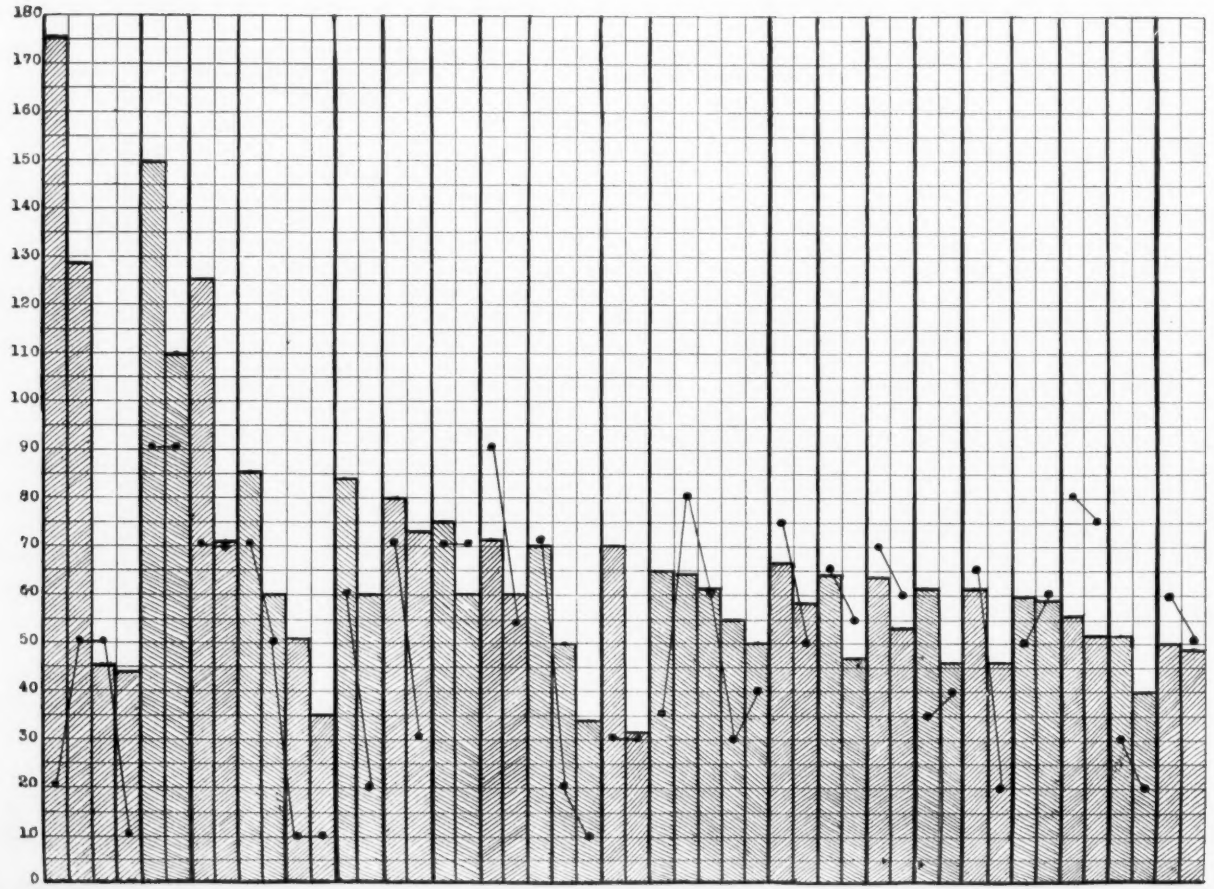

Chart 10.—Motility on repeated examinations of same people; each group of columns (cubic centimeters) represents highest volume reached in stomach on successive tests of one person; dots represent emptying time (minutes).

not yet clearly known. Anatomic disease of the stomach (carcinoma, severe gastritis, etc.) probably does, but it seems equally clear that minor extra-abdominal disorders do not. One may raise the question, too, of whether the terms hypernormal, normal, hyponormal and hyperacidity are satisfactory as they have clinical implications that do not appear altogether warranted. It might be better to speak simply of low, average and relatively high acidities. One may emphasize, too, the absence of any definite relation between volume of secretion and acidity.

Motility, on the other hand, was found in this group to be very variable. The same individual may empty his stomach within a few minutes on one occasion and later accumulate a large volume of gastric contents which is discharged only after a long interval. This question will be more fully discussed in another article.

Chart 10.—Motility on repeated examinations of same people; each group of columns (cubic centimeters) represents highest volume reached in stomach on successive tests of one person; dots represent emptying time (minutes).

CONCLUSIONS

1. The volume of gastric juice secreted by people without digestive symptoms in response to a standard stimulus varied between 9 and 69 cc. for a ten minute period.

2. Seventy-three per cent of the group secreted from 10 to 30 cc. in a ten minute period.

3. Highest acidity of the gastric contents (titratable) varied from 0 to 118. All degrees between these extremes were encountered.

4. No relation was found between volume of juice secreted and acidity.

5. The motility of the stomach in different people varied widely and bore no relation to volume of secretion or to acidity.

6. On repeated examinations of the same person acidity and volume of secretion were practically constant; motility varied greatly.

HYPERTENSION AND CONSTIPATION

A STATISTICAL INQUIRY *

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R. L. McCALLA, M.D.
AND
A. ZIMMERMANN, DR.ÈS.SC.
SAN FRANCISCO

It is commonly assumed by practicing physicians that "intestinal autointoxication" has something to do with the production of hypertension. The more thoughtful writers on the subject, knowing that there is no mass of statistics to which they can turn for enlightenment, are guarded in their statements, but those who live by washing colons, and those who have for sale laxative drugs and foods and patented syringes have no such inhibitions. They proclaim from the housetops that one of the dire consequences of constipation is high blood pressure, and to a large extent their propaganda is believed.

It seemed wise, therefore, to study the problem statistically; that is, to compare the pressures of several hundred men and women with normal bowels with those of several hundred constipated individuals. It is really hard to understand why, during the course of years of argument on the subject, so simple a thing has not been done.

In this study we have analyzed the records of 410 men and 585 women, office patients of one of us (W. C. A.). Of these, 436 were classed as normal, 414 as habitually constipated, 110 as having occasional or recent constipation, and thirty-five as having diarrhea.

We have analyzed separately the data from men and women, because their standards of pressure are quite different. We have also had to take into account the age and weight distributions of the various groups in order to make the necessary corrections in the averages that we present here. Without such corrections our results might be misleading because we cannot offhand compare the mean pressures in any two groups. If one group should happen to be made up largely of young, thin persons and the other mainly of old, stout persons, other things being equal, the second group would have to have a much higher average pressure than the first. To be sure, we ordinarily do not meet with such extreme disparities in the age and weight composition of groups, but the disparities that we do regularly encounter not infrequently account for all the difference that we get between two uncorrected means.

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* From the George Williams Hooper Foundation for Medical Research and the Department of Medicine, University of California Medical School.

The method of making the correction in data from women has been described in a recent article by Alvarez and Zimmermann.[1] In this article we supply the necessary standards for the age and weight correction in men. These standards unfortunately are based on a rather small group, but so far as we know, they are the only ones yet available for our purpose. The figures prepared by the insurance companies do

TABLE 1.—*Blood Pressure in Men, by Age Groups; Standards for the Age Correction*

	Age									
	16 to 29		30 to 39		40 to 49		50+		All Ages	
Blood Pressure	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent
From 90 to 94	..	....	1	0.8	1	0.9	1	0.9	3	0.7
95 to 99	1	1.5	1	0.8	1	0.9	2	1.8	5	1.2
100 to 104	2	3.0	3	2.3	3	2.6	..	....	8	1.9
105 to 109	5	7.5	5	3.8	3	2.6	3	2.7	16	3.8
110 to 114	4	6.0	10	7.5	6	5.3	5	4.5	25	5.9
115 to 119	7	10.4	13	9.8	10	8.8	8	7.3	38	9.0
120 to 124	11	16.4	18	13.5	11	9.6	11	10.0	51	12.0
125 to 129	5	7.5	20	15.0	14	12.3	3	2.7	42	9.9
130 to 134	7	10.4	17	12.8	19	16.6	11	10.0	54	12.7
135 to 139	6	9.0	12	9.0	8	7.0	6	5.4	32	7.6
140 to 144	7	10.4	10	7.5	12	10.5	11	10.0	40	9.5
145 to 149	8	11.9	5	3.8	7	6.1	5	4.5	25	5.9
150 to 154	1	1.5	8	6.0	6	5.3	8	7.3	23	5.4
155 to 159	1	1.5	4	3.0	2	1.8	5	4.5	12	2.8
160 to 164	..	...	2	1.5	5	4.4	12	10.9	19	4.5
165 to 169	..	...	3	2.3	2	1.7	4	3.6	9	2.1
170 to 174	1	1.5	..	...	1	0.9	2	1.8	4	0.9
175 to 179	..	...	..	...	1	0.9	4	3.6	5	1.2
180 to 184	..	...	..	...	1	0.9	1	...	2	0.5
185 to 189	..	...	..	...	1	0.9	3	2.7	4	0.9
190 to 194	1	1.5	..	...	..	...	1	0.9	2	0.5
195 to 199	..	...	..	...	..	...	1	0.9	1	0.2
200 to 204	..	...	..	...	..	...	..	....	..	...
205 to 209	..	...	..	...	..	...	1	0.9	1	0.2
210 to 214	..	...	..	...	..	...	..	....	..	...
215 to 219	..	...	..	...	..	...	1	0.9	1	0.2
220 to 224	..	...	..	...	..	...	..	....	..	...
225 to 229	..	...	..	...	..	...	..	....	..	...
230 to 234	..	...	..	...	..	...	1	0.9	1	0.2
235 to 239	..	...	..	...	..	...	..	....	..	...
240 to 244	..	...	1	0.8	..	...	..	....	1	0.2
245 to 249	..	...	..	...	..	...	..	....	..	...
Total.....	67	15.8	133	31.4	114	27.0	110	25.8	424	....
Mean.....	129.4		130.5		133.4		144.1		134.7	
S. D.....	16.8		17.9		17.8		25.7		21.0	
P. E. of mean	1.4		1.0		1.1		1.7		0.7	

not help us because they are based only on accepted cases and not on the population as we find it.

As a description of the arithmetic used in getting the correction factors makes almost unintelligible reading, we must ask the inquiring student to consult the article mentioned. The basic principles underlying the process will be found in chapter 9 of Pearl's "Medical Biometry and Statistics."

1. Alvarez, W. C., and Zimmermann, A.: Blood Pressure in Women as Influenced by the Sexual Organs, Arch. Int. Med. **37**:597 (May) 1926.

BLOOD PRESSURE STANDARDS IN MEN

Table 1 shows a few interesting things. We notice that the averages for the four age groups are 129.4 ± 1.4, 130.5 ± 1.0, 133.4 ± 1.1, and 144.1 ± 1.7. These findings agree with those made on university students [2] in showing that the blood pressure does not rise in men up to the age of 40 and little up to the age of 50. The definite rise comes after 50. It is of interest to compare these averages with those found in women,

TABLE 2.—*Blood Pressure in Men; Standards for the Weight Correction, All Ages*

Blood Pressure	Build					
	Thin		Normal		Stout	
	F	Per Cent	F	Per Cent	F	Per Cent
From 90 to 94	3	3.5	..	....	..	....
95 to 99	1	1.1	4	1.6	..	....
100 to 104	3	3.5	6	2.3	..	....
105 to 109	5	5.7	10	3.9	1	1.7
110 to 114	9	10.3	15	5.8	2	2.4
115 to 119	16	18.4	23	9.0	..	....
120 to 124	15	17.3	32	12.5	6	7.1
125 to 129	7	8.0	29	11.3	8	9.4
130 to 134	9	10.3	31	12.1	16	18.8
135 to 139	1	1.1	23	9.0	7	8.2
140 to 144	6	6.9	27	10.5	6	7.1
145 to 149	3	3.5	14	5.5	6	7.1
150 to 154	2	2.3	10	3.9	11	13.0
155 to 159	1	1.1	9	3.5	4	4.7
160 to 164	..	....	10	3.9	4	4.7
165 to 169	3	3.5	1	0.4	5	5.9
170 to 174	1	1.1	3	1.2	2	2.4
175 to 179	..	....	4	1.6	1	1.7
180 to 184	1	1.1	1	0.4	..	....
185 to 189	1	1.1	3	1.2	..	....
190 to 194	..	....	..	....	2	2.4
195 to 199	..	....	..	....	1	1.7
200 to 204	..	....	..	....	..	....
205 to 209	..	....	..	....	1	1.7
210 to 214	..	....	..	....	..	....
215 to 219	..	....	..	....	1	1.7
220 to 224	..	....	..	....	..	....
225 to 229	..	....	..	....	..	....
230 to 234	..	....	1	0.4	..	....
235 to 239	..	....	..	....	..	....
240 to 244	..	....	..	....	1	1.7
245 to 249	..	....	..	....	..	....
Total.....	87	20.2	256	60.0	85	19.8
Mean.....		125.7		133.1		146.3
S. D.		18.8		18.9		23.0
P. E. of mean		1.4		0.8		1.7

in whom the figures are 122.1 ± 0.8, 125.8 ± 0.8, 135.3 ± 1.2, 154.4 ± 1.7. Figure 1 shows how, in the twenties, the pressures of the women average 10 mm. lower than those of the men and after 50 they average 10 mm. higher than the men. The average for all ages put together is practically the same in both sexes, that is, 134.5 ± 0.7 for the women, and 134.7 ± 0.7 for the men.

2. Alvarez, W. C.: Blood Pressures in 15,000 University Freshmen, Arch. Int. Med. **32**:17 (July 15) 1923.

Table 2 shows that the pressures of those with a normal build and weight average some 8 mm. higher than do those for the thin; and the pressures of the fat average 13 mm. higher than do those of the normal.

All the pressures were taken with the auscultatory method, with a mercury manometer and a standard cuff. The patients were reclining. If the pressure varied much, we used the mode of several readings made on the same or subsequent days.

TABLE 3.—*Women, All Ages*

	Normal Bowels		Chronic Constipation		Occasional and Recent Constipation		Diarrhea	
Blood Pressure	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
From 90 to 94	..	....	..	....	..	....	..	....
95 to 99	2	0.8	2	0.8	1	1.8	..	....
100 to 104	4	1.5	6	2.4	2	3.6	..	....
105 to 109	7	2.6	8	3.2	2	3.6	..	....
110 to 114	17	6.4	21	8.5	4	7.3	3	17.6
115 to 119	25	9.5	27	10.9	7	12.7	..	....
120 to 124	26	9.9	25	10.1	3	5.5	7	41.1
125 to 129	24	9.1	31	12.5	6	10.8	..	....
130 to 134	32	12.1	28	11.3	4	7.3	1	5.9
135 to 139	22	8.3	17	6.8	3	5.5	..	....
140 to 144	23	8.7	18	7.3	7	12.7	5	29.5
145 to 149	15	5.7	7	2.8	1	1.8	..	....
150 to 154	11	4.2	15	6.0	2	3.6	1	5.9
155 to 159	11	4.2	9	3.6	3	5.5	..	....
160 to 164	6	2.3	1	0.4	4	7.3	..	....
165 to 169	4	1.5	6	2.4	2	3.6	..	....
170 to 174	5	1.9	5	2.1	..	....	..	....
175 to 179	7	2.6	6	2.4	1	1.8	..	....
180 to 184	5	1.9	6	2.4	..	....	..	....
185 to 189	3	1.1	1	0.4	1	1.8	..	....
190 to 194	1	0.4	3	1.2	1	1.8	..	....
195 to 199	1	0.4	..	....	1	1.8	..	....
200 to 204	2	0.8	1	0.4	..	....	..	....
205 to 209	3	1.1	1	0.4	..	....	..	....
210 to 214	1	0.4	2	0.8	..	....	..	....
215 to 219	1	0.4	1	0.4	..	....	..	....
220 to 224	3	1.1	..	....	..	....	..	....
225 to 229	1	0.4	..	....	..	....	..	....
230 to 234	..	....	2	0.8	..	....	..	....
235 to 239	..	....	..	....	..	....	..	....
240 to 244	..	....	..	....	..	....	..	....
245 to 249	..	....	..	....	..	....	..	....
250+	2	0.8	..	....	..	....	..	....
Total.....	264	....	249	....	55	....	17	....
Mean.....	140.0		136.0		136.4		131.0	
Mean corrected..	141.4		137.1		135.3		133.5	
S. D.....	27.2		24.5		23.1		12.3	
P. E. of mean....	1.1		1.0		2.1		2.0	

Corrections for age and weight:

Normal bowels..... $140.0 \pm 1.1 \times 1.009 \times 1.0007 = 141.4 \pm 1.1$

Chronic constipation..... $136.0 \pm 1.0 \times 1.004 \times 1.004 = 137.1 \pm 1.0$

Occasional and recent constipation..... $136.4 \pm 2.1 \times 1.000 \times 0.992 = 135.3 \pm 2.1$

Diarrhea..... $131.0 \pm 2.0 \times 1.015 \times 1.004 = 133.5 \pm 2.0$

BLOOD PRESSURE IN NORMAL, CONSTIPATED AND DIARRHEIC PERSONS

Tables 3 and 4 show the distribution of the data from the subjects in the four groups of normal, constipated, occasionally or recently constipated, and occasionally or recently diarrheic. These patients were all ambulant, all white, and for the most part from the middle and upper walks of life. Most of them came seeking relief from gastro-intestinal troubles.

The letters S.D. represent the standard deviation which is a measure of the scattering of the figures in the distribution. The P.E., or probable error, of the mean is a most useful figure as it gives us an idea of the reliability of our averages. When, as in the case of the diarrheic patients, the group is small, we know we cannot argue very far on the basis of the means that we get. The figures 136.0 ± 3.2 mean that if we were to study another 10,000 cases, the odds are even that the average we would then obtain would lie somewhere between 139.2 and 132.8. In figure 2 we have shown the extent of the minus P.E. by cutting a nick out of the end of each column.

The value of this P.E. will be seen again when we come to appraise the significance of a difference between two means. The P.E. of a difference is the square root of the sum of the squares of the P.E.'s of

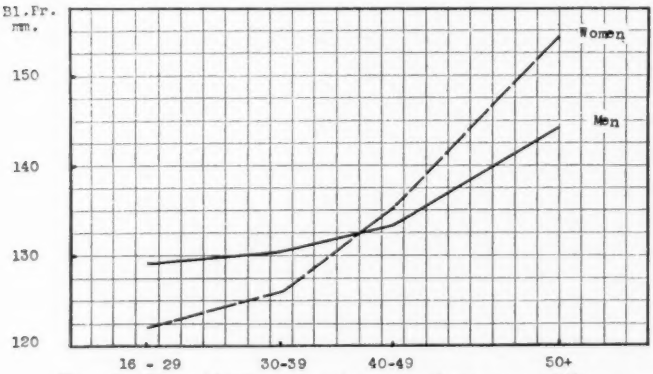

Chart 1.—Mean blood pressure in men and women at different ages.

the two measures being compared. If the difference is little larger than its probable error, we naturally can put little confidence in it. If it is 4 or 5 times as large as its P.E., it is almost certainly significant.

On turning, then, to figure 2, we see that among the men there is no signficant difference between the pressures in the normal, the constipated, and the diarrheic. Among the women, strange to say, those with constipation average 4.3 mm. lower than the normal. This difference is 2.9 times its P.E., which means that the odds are 18.8 to 1 that there is some significance behind it. It would be a hard blow to the apostles of autointoxication if it should turn out that a certain amount of constipation is good for a woman. The puzzling feature is that those with occasional or recent constipation have an even lower average pressure. We note, however, that there were only fifty-five in that group and the P.E. is 2.1 mm., so that, with a larger number of cases, the difference might be wiped out.

Some of the believers in intestinal poisoning may now assert that the blood pressure has been lowered in the constipated group by histamin-like toxins, but that will not explain why it did not happen in the men. Another difficulty in interpretation arises from the fact that one might just as well argue that hypertension has, perhaps, a slightly laxative effect on women. Some studies which we hope to publish soon show

TABLE 4.—*Men, All Ages*

	Normal Bowels		Chronic Constipation		Occasional and Recent Constipation		Diarrhea	
Blood Pressure	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
From 90 to 94	1	0.6	1	0.6	1	1.8	..	....
95 to 99	4	2.3	1	0.6	..	....	..	....
100 to 104	2	1.2	3	1.8	1	1.8	..	....
105 to 109	7	4.1	6	3.6	2	3.6	..	....
110 to 114	6	3.5	13	7.9	5	9.1	4	22.2
115 to 119	14	8.1	16	9.7	2	3.6	..	....
120 to 124	20	11.6	18	10.9	9	16.3	5	27.8
125 to 129	20	11.6	13	7.9	7	12.7	..	....
130 to 134	24	14.0	18	10.9	10	18.2	3	16.6
135 to 139	16	9.3	9	5.5	5	9.1	..	....
140 to 144	16	9.3	18	10.9	4	7.3	2	11.1
145 to 149	10	5.8	10	6.0	4	7.3	..	....
150 to 154	11	6.4	10	6.0	1	1.8	1	5.6
155 to 159	5	2.9	3	1.8	2	3.6	..	....
160 to 164	7	4.1	9	5.5	1	1.8	1	5.6
165 to 169	4	2.3	5	3.1	..	....	..	....
170 to 174	1	0.6	4	2.4	..	....	1	5.6
175 to 179	1	0.6	1	0.6	..	....	..	....
180 to 184	..	....	2	1.2	..	....	1	5.6
185 to 189	1	0.6	1	0.6	1	1.8	..	....
190 to 194	1	0.6	1	0.6	..	....	..	....
195 to 199	..	....	1	0.6	..	....	..	....
200 to 204	..	....	..	....	..	....	..	....
205 to 209	..	....	1	0.6	..	....	..	....
210 to 214	..	....	..	....	..	....	..	....
215 to 219	1	0.6	..	....	..	....	..	....
220 to 224	..	....	..	....	..	....	..	....
225 to 229	..	....	..	....	..	....	..	....
230 to 234	..	....	1	0.6	..	....	..	....
235 to 239	..	....	..	....	..	....	..	....
240 to 244	..	....	..	....	..	....	..	....
245 to 149	..	....	..	....	..	....	..	....
Total.....	172	....	165	....	55	....	18	....
Mean.....	133.9		136.2		130.2		136.2	
Mean corrected..	134.0		136.0		134.5		136.1	
S. D.	18.8		22.3		15.1		20.3	
P. E. of mean....	1.0		1.2		1.4		3.2	

Corrections for age and weight:

Normal bowels..... $133.9 \pm 1.0 \times 1.007 \times 0.994 = 134.0 \pm 1.0$

Chronic constipation..... $136.2 \pm 1.2 \times 0.995 \times 1.004 = 136.0 \pm 1.2$

Occasional and recent constipation..... $130.2 \pm 1.4 \times 1.008 \times 1.025 = 134.5 \pm 1.4$

Diarrhea..... $136.2 \pm 3.2 \times 0.996 \times 1.004 = 136.1 \pm 3.2$

that this is not at all improbable, and that there are certain conditions which, while not laxative enough to produce diarrhea, are laxative enough to insure a high percentage of individuals with normal bowel movements. The low pressures found in women with diarrhea might easily be due to a slight debilitating effect from that condition. Against that interpretation is the fact that there is no lowering of the pressures in the diarrheic men. Unfortunately, the diarrheic groups are so small

that we must withhold discussion until more data are gathered. As the senior writer has shown elsewhere [3] if autointoxication is ever a factor in disease production we should expect to find it in the diarrheas in which the intestinal contents are liquid, the bacteria active, and the mucous membrane damaged.

INCIDENCE OF CONSTIPATION AT DIFFERENT AGES

The percentages given in the upper part of table 5 would have thrown some light on the incidence of constipation in men and women if we had been able to take the records as they came. Unfortunately, there

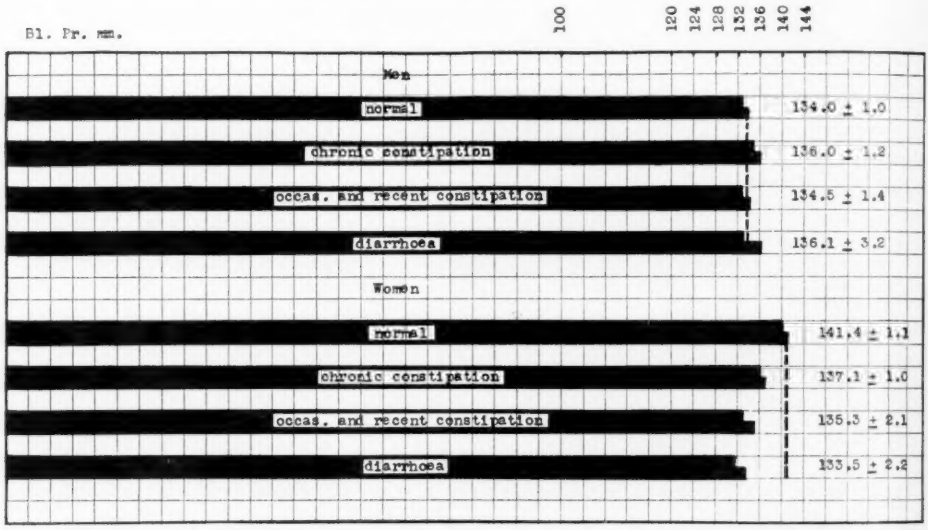

Chart 2.—Mean pressures of men and women with normal bowels, constipation and diarrhea; the nick in the end of the column represents the minus probable error.

were so few women with normal bowels that we had to pick over several hundred histories to get out the 264 that we needed to compare with the 249 with constipation.

The one interesting point that we would comment on is that the men have little constipation in youth. They get theirs late in life while the women have the most trouble in their thirties.

SUMMARY

A statistical analysis shows that in men constipation has absolutely no effect on the blood pressure. In women, there is a pretty definite

3. Alvarez, W. C.: Intestinal Autointoxication, Physiol. Rev. **4**:352 (July) 1924.

TABLE 5.—*Age Distribution*

Age Groups	Normal Bowels				Chronic Constipation				Occasional and Recent Constipation				Diarrhea			
	Women		Men		Women		Men		Women		Men		Women		Men	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
16 to 29	75	28.4 ± 1.9	32	18.6 ± 2.0	52	20.9 ± 1.8	14	8.5 ± 1.5	11	20.0 ± 3.6	15	27.3 ± 3.7	5	29.4 ± 5.0	3	16.6 ± 5.9
30 to 39	76	28.8 ± 1.9	53	30.8 ± 2.4	84	33.8 ± 2.0	53	32.0 ± 2.5	19	34.5 ± 4.3	19	34.5 ± 4.3	6	35.2 ± 7.8	7	38.9 ± 7.8
40 to 49	51	19.3 ± 1.6	54	31.4 ± 2.4	53	21.2 ± 1.8	48	29.0 ± 2.4	10	18.2 ± 3.5	9	16.4 ± 3.5	2	11.8 ± 5.3	2	11.1 ± 5.0
50+	62	23.5 ± 1.8	33	19.2 ± 2.0	60	24.1 ± 1.8	50	30.5 ± 2.4	15	27.3 ± 3.7	12	21.8 ± 3.6	4	23.5 ± 6.9	6	33.4 ± 7.5
Total	264		172		249		165		55		55		17		18	

Weight Distribution

Body Build	Normal Bowels				Chronic Constipation				Occasional and Recent Constipation				Diarrhea			
	Women		Men		Women		Men		Women		Men		Women		Men	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Thin	62	23.5 ± 1.8	24	14.0 ± 1.8	63	25.2 ± 1.9	31	18.7 ± 2.0	11	20.0 ± 3.6	16	29.0 ± 4.0	4	23.5 ± 6.9	3	16.7 ± 5.9
Normal	147	55.7 ± 2.1	105	61.0 ± 2.5	140	56.2 ± 2.1	104	63.0 ± 2.5	29	52.7 ± 4.5	37	67.0 ± 4.3	10	58.9 ± 8.1	12	66.6 ± 7.5
Stout	55	20.8 ± 1.7	43	25.0 ± 2.2	46	18.6 ± 1.7	30	18.3 ± 2.0	15	27.3 ± 3.7	2	4.0 ± 1.7	3	17.6 ± 6.2	3	16.7 ± 5.9
Total	264		172		249		165		55		55		17		18	

connection between constipation and a slightly lower mean blood pressure. It is possible that diarrhea is also associated with a lower pressure but our data are too few for a trustworthy conclusion.

It must be remembered in studying these data that there are three possible interpretations. The constipation may lower the pressure; lower pressures may cause the constipation, and higher pressure may be slightly laxative.

Standards are given for the correction of averages according to differences in age and weight distribution. It is seen that in men the blood pressure does not rise appreciably until after the age of 50. Blood pressure in women behaves differently.

Men with normal weight average 10 mm. higher than do the lean, and the stout average 13 mm. higher than the normal.

DISEASES OF THE LIVER

V. A COMPARATIVE STUDY OF TESTS FOR HEPATIC FUNCTION IN CERTAIN DISEASES OF THE HEMATOPOIETIC SYSTEM *

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The recent experiments of Mann, Bollman and Magath [1] have shown that a dog will become jaundiced after the complete extirpation of the liver and that the injection of hemoglobin increases the rapidity with which the icterus develops. These observations indicate that the liver must be considered, at least to some extent, as an excretory organ for the bile pigments. The physiologic possibility of a true hemolytic jaundice of extrahepatic origin, a point that heretofore has not met with universal acceptance, must be recognized. The observations of van den Bergh,[2] Lepehne,[3] McNee,[4] Feigl and Querner [5] and others on the changes in the van den Bergh reaction in cases of hemolytic jaundice have further served to emphasize the importance of a more accurate knowledge of the activity of the liver.

Jaundice may be produced by three separate pathologic processes: (1) by a mechanical obstruction to the extrahepatic biliary passages with resultant resorption of bile pigments (so-called obstructive jaundice); (2) by the inability of the parenchymal cells of the liver to excrete the bile pigments in the normal manner (so-called hepatic jaundice), and (3) by destruction of erythrocytes and the formation of bilirubin more rapidly than normally, with consequent retention in the blood stream (so-called hemolytic or hematogenous jaundice).

We have previously reported a comparative study of certain tests of hepatic function in the different varieties of obstructive jaundice. We now report the results of a similar study in a carefully selected series

* From the Section on Medicine, Mayo Clinic.

1. Mann, F. C.; Bollman, J. L., and Magath, T. B.: Studies on the Physiology of the Liver: IX, The Formation of Bile Pigment After Total Removal of the Liver, Am. J. Physiol. **69**:393-409 (July) 1924.

2. Van den Bergh, A. A. H.: Der Gallenfarbstoff im Blute, Leiden, S. C. van Doesburgh **8**, 1918.

3. Lepehne, Georg: Untersuchungen über Gallenfarbstoff im Blutserum des Menschen, Deutsches Arch. f. klin. Med. **132**:96-120 (April) 1920; **135**:79-107 (Jan.) 1921.

4. McNee, J. W.: Jaundice: A Review of Recent Work, Quart. J. Med. **16**: 390-420 (July) 1923.

5. Feigl, J., and Querner, E.: Bilirubinämie in ihren physiologisch-chemischen Beziehungen mit besonderer Berücksichtigung der diagnostischen Bedeutung, Ztschr. f. d. ges. exper. Med. **9**:153-250, 1919.

of cases of hemolytic jaundice and certain other diseases of the hematopoietic system. The theoretic basis of the different tests and the details of the technic used are given in the initial paper of this series.[6] In order more fully to correlate the functional studies with the clinical picture it seems desirable to include a short summary of the principal clinical features of the different conditions studied. Abstracts of the histories of typical cases are given in more detail. Only significant laboratory data are included in these abstracts but the complete findings are given in the accompanying tables. The phenoltetrachlorphthalein test is reported in terms of the hour reading.

HEMOLYTIC JAUNDICE

The "hematogenous" jaundice of the older writers was originally descriptive of those cases in which icterus was present without manifest obstruction in the bile passages. The acceptance and use of this term has varied widely with the various theories regarding the rôle of the liver in the formation of bile pigment. The experiments of Whipple and Hooper [7] and the recent studies of Mann, Bollman and Magath on dehepatized animals, showing the extrahepatic formation of bilirubin, afford the basis for the recognition of hemolytic jaundice as a distinct clinical and physiologic entity.

The characteristic features of this condition have recently been discussed by Tileston [8] and Meulengracht.[9] These include long continued icterus of moderate intensity without the pruritus or bradycardia characteristic of obstructive jaundice. The urine contains urobilin but no bile, while the stools are highly colored. The spleen is enlarged. Moderate anemia may be present. A marked feature is the presence of gallstone attacks, which are often assumed to be the cause of the icterus and may lead to operation;[10] gallstones were present in 58 per cent of the cases at the Mayo Clinic in which splenectomy was performed. Most characteristic are the diminished resistance of the erythrocytes to hemolysis by hypotonic solution of sodium chloride and the presence of large numbers of reticulated red cells. We have not attempted the discussion separately of the congenital, or Minkowski-Chauffard, and the acquired, or Hayem-

6. Greene, C. H.; Snell, A. M., and Walters, Waltman: Diseases of the Liver: I, A Survey of Tests for Hepatic Function, Arch. Int. Med. **36**:248-272 (Aug.) 1925.

7. Whipple, G. H., and Hooper, C. W.: Icterus: A Rapid Change of Hemoglobin to Bile Pigment in the Circulation Outside the Liver, J. Exper. Med. **17**:612-635, 1913. Whipple, G. H.: The Origin and Significance of the Constituents of the Bile, Physiol. Rev. **2**:440-459 (July) 1922.

8. Tileston, W.: Hemolytic Jaundice, Medicine **1**:355-388 (Aug.) 1922.

9. Meulengracht, E.: Der chronische hereditäre hämolytische Ikterus (konstitutionelle Hypersplenie), Leipzig, W. Klinkhardt, 1922.

10. Giffin, H. Z.: Hemolytic Jaundice: A Review of Seventeen Cases, Surg. Gynec. Obst. **25**:152-161 (Aug.) 1917.

Widal, forms of the condition. The majority of the cases belonged to the former group. The results of the different functional tests are shown in table 1.

CASE 1 (case 7, table 1).—A young man, aged 21, was admitted to the clinic, March 10, 1924, because of icterus and a left abdominal mass. One brother had been jaundiced, had had an enlarged spleen since childhood, and died at the age of 18 from an acute illness accompanied by fever and jaundice. The patient had been lemon yellow since the age of 3. For three years previous to admission he had had irregular gastro-intestinal upsets with nausea, vomiting and slight jaundice, but no colic. In January, 1925, he had a more severe attack, with vomiting, diarrhea, fever and jaundice for several days. An enlarged spleen was discovered at that time.

He was slightly icteric in appearance. The liver could not be felt although the spleen was slightly enlarged. The urine contained urobilin but no bile. The blood showed a marked secondary type of anemia with an increase in the fragility of the red cells. The differential leukocyte count was normal, but 23.1 per cent of reticulated erythrocytes were present. The serum bilirubin was 3.3 mg. for each hundred cubic centimeters of blood. There was no retention of phenoltetrachlorphthalein.

At operation, March 27, an enlarged spleen was removed. Chronic cholecystitis with multiple cholelithiasis was discovered and the gallbladder was excised, April 9. The jaundice rapidly disappeared and the postoperative recovery was uneventful.

PERNICIOUS ANEMIA

The clinical picture is well known.[11] Increasing emphasis is placed on the evidence of augmented destruction of blood. The lemon color of the patient, the presence of urobilin and urobilinogen in the urine, and pleochromia in the bile, as emphasized by Schneider,[12] and particularly by Giffin, Sanford and Szlapka,[13] are evidence of increased destruction of the blood. The varying relationship between the deficient formation of red blood cells and their excessive destruction seems to determine the condition of the blood at any particular time. The frequency with which the liver and spleen are enlarged indicates the importance of further knowledge concerning functional changes. The laboratory findings in a series of typical cases are given in table 1.

CASE 2. (Case 8, table 1).—A man, aged 59, developed a case of pernicious anemia with hemolytic crisis following transfusion. He first came to the clinic, Dec. 18, 1920, because of weakness and anemia of two months' duration. He was pale yellow. The spleen was palpable. The erythrocytes numbered 1,880,000, the leukocytes 2,600, and the hemoglobin was 28 per cent. Gastric achlorhydria was present and duodenal drainage showed an increase in the pigments in the bile. A

11. Minot, G. R.: Clinical Discussion of the Anemias, Oxford Medicine **2**:611-635, 1920.

12. Schneider, J. P.: The Splenic Pathology of Pernicious Anemia and Allied Conditions: A Duodenal Method of Estimating Hemolysis, Arch. Int. Med. **17**:32-41 (Jan.) 1916; Further Quantitative Study of the Duodenal Blood-Derived Pigments, Arch. Int. Med. **19**:156-162 (Jan.) 1917.

13. Giffin, H. Z.; Sanford, A. H., and Szlapka, T. L.: The Estimation of Urobilin and Urobilinogen in the Duodenal Contents, Am. J. M. Sc. **155**:562-579 (April) 1918.

TABLE 1.—*Hemolytic Icterus*

Case	Date	Age, Years	Sex*	Edge of Liver Palpable, Cm.	Jaundice	Spleen Enlarged, Grade 0 to 4	Urine: Urobilin	Urine: Bile Pigments	Blood Count: Hemoglobin, %	Blood Count: Erythrocytes, Millions	Blood Count: Leukocytes	Blood Count: Reticulated Erythrocytes, per Cent	Fragility Test: Sodium Chloride, per Cent: Initial Hemolysis	Fragility Test: Sodium Chloride, per Cent: Complete Hemolysis	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Nonprotein Nitrogen	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Urea	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Uric Acid	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Creatinine	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Amino-Acid Nitrogen	Bile Pigments (Serum): Bile Index	Bile Pigments (Serum): Serum Bilirubin, Mg. per 100 Cc.	Bile Pigments (Serum): Van den Bergh Direct Reaction	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: Normal	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: 1 Hour	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: 2 Hours	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: Change	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 15 Minutes	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 1 Hour	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 2 Hours	Phenoltetrachlorphthalein: Dye in Urine, Mg.	Comment
1	5/23/23	24	♀	0	1	0	+	0	80	5.20	9,600	....	0.40	0.32	..	..	..	..	..	27	7.7	+	..	..	..	..	14	8	6	0.5	Mild case; no operation
2	5/31/24	35	♀	3	1	3	+	0	76	4.47	4,300	....	0.46	0.36	55	27	3.2	2.0	6.5	..	4.9	±	75	78	71	3	11	6	3	0.9	Splenectomy
3	1/13/25	22	♀	0	1	2	+	0	51	2.63	9,100	25.0	0.50	0.38	..	35	3.3	1.1	...	13	4.6	0	..	..	..	..	10	6	..	2.5	Splenectomy
4	8/16/23	31	♀	0	2	2	+	0	37	2.20	12,600	16.2	0.50	0.38	..	28	...	...	...	..	...	..	..	..	..	..	12	4	1	0.0	Liver in good condition; splenectomy
5	7/10/25	21	♂	0	1	2	..	..	54	3.17	7,800	....	0.50	0.38	40	22	...	...	6.1	..	5.7	0	77	88	84	11	7	2	1	...	Splenectomy; multiple cholelithiasis
6	6/20/25	22	♂	0	1	0	+	..	76	4.94	5,200	....	0.42	0.32	..	27	4.1	1.5	...	..	4.6	0	82	92	84	10	5	2	0	...	Mild case; no operation
7	3/12/25	21	♂	0	1	1	+	0	48	2.84	10,400	23.1	0.50	0.34	..	23	3.9	1.0	...	..	3.3	0	..	..	..	..	..	2	1	0.4	Splenectomy; multiple cholelithiasis
																															Pernicious Anemia
8	3/18/24	63	♂	4	4	1	..	..	14	0.88	1,600	....	....	....	115	121	10.6	3 0	7.4	87	26.2	+	...	...	...	..	24	24	22	...	Hemolytic crisis with jaundice following transfusion
9	3/19/24	53	♀	†	0	1	+	..	30	1.76	1,500	....	....	....	..	..	...	...	...	14	5.0	±	...	...	...	..	..	8	..	0.5	Pernicious anemia
10	3/30/25	57	♀	†	0	0	+	..	44	2.37	5,000	....	....	....	..	35	4.2	1.1	...	..	3.0	0	100	...	...	..	7	8	2	0.5	
11	2/29/24	57	♀	0	0	0	+	..	70	3.76	5,000	....	....	....	31	34	...	...	...	6	1.6	0	100	117	108	17	10	3	0	0.6	
12	4/15/24	45	♀	0	0	..	+	..	42	1.90	6,100	....	....	....	27	38	4.1	1.5	5.9	9	3.3	0	...	...	...	..	7	3	2	0.0	
13	3/22/24	44	♀	0	0	0	+	..	54	2.27	6,100	....	....	....	36	33	3.5	1.8	6.2	8	3.0	0	83	103	89	20	6	3	0	0.3	
14	1/27/25	65	♀	15	0	0	+	..	25	1.04	5,800	....	....	....	..	34	...	...	...	..	2.4	0	..	...	...	..	5	1	0	0.0	
15	3/14/24	44	♀	†	0	0	+	..	52	2.11	5,000	....	....	....	34	24	...	...	6.1	5	2.2	0	91	110	96	19	4	2	0	0.5	
16	1/ 8/24	70	♀	0	0	0	+	..	40	1.81	7,000	....	....	....	43	42	...	...	...	6	1.5	0	103	110	105	7	4	1	0	0.3	
17	2/11/24	40	♀	0	0	0	..	..	47	2.21	2,700	....	....	....	27	27	...	...	...	..	2.0	0	90	110	86	20	4	0	0	0.0	
18	2/16/25	39	♀	†	0	1	+	..	25	1.32	3,200	....	....	....	..	27	...	...	...	..	2.6	0	..	...	..	..	3	1	0	0.0	
19	2/20/24	53	♀	0	0	0	+	..	58	2.23	5,200	....	....	....	27	29	...	...	...	5	1.4	0	..	...	..	..	3	0	0	0.0	

* In this and the following tables, ♂ indicates male, ♀ female; †, just palpable; §, markedly enlarged; ‡ + indicates a "prompt" direct reaction; ±, "delayed" direct reaction, and 0, an indirect reaction.

diagnosis of pernicious anemia was made at that time. In the succeeding three and one-half years he was under close observation, the disease following a typical course with frequent remissions. He received a total of forty-eight transfusions during this period.

He returned, March 10, 1924 (the eleventh time). Ten days before he had suddenly become much weaker, and the anemia more marked. He was lemon yellow. The spleen was palpable but the liver could not be felt. A small amount of free fluid was present in the abdomen. The erythrocytes numbered 870,000, the leukocytes 3,900, and the hemoglobin was 18 per cent. He was given three transfusions of 250 cc. each during the succeeding week.

Following the second transfusion, jaundice developed and increased rapidly in intensity. March 18, two days after the last transfusion, the erythrocytes numbered 880,000, the leukocytes 1,600, and the hemoglobin was 14 per cent. The jaundice was marked. The liver was enlarged and the edge could be felt 4 cm. below the costal margin. The serum bilirubin was 26.2 mg. for each hundred cubic centimeters of blood. There was retention of phenoltetrachlorphthalein, with a reading of 24 per cent. The urine contained albumin and bile, but no casts. The urinary output varied between 700 and 1,200 cc. daily at this time. The blood urea was 122 mg. Improvement followed the initial hemolytic crisis. The jaundice disappeared and the blood urea fell to 52 mg. by April 5. This improvement was only temporary and the patient died a week later with evidence of myocardial failure. Necropsy was not permitted.

The similarity is striking between the changes associated with the hemolytic crisis in this patient and the artificial hemolytic crisis produced by the therapeutic use of phenylhydrazine.

Case 3 (case 12, table 2).—A man, aged 45, was admitted to the clinic, April 15, 1924, because of weakness and loss of strength during the preceding year. Ten years before, he had had a sore tongue, and gastric achlorhydria was discovered at that time. The sore tongue recurred irregularly but he was not too ill to work. In 1923, he began to lose weight; pallor was pronounced and he became very weak, with dyspnea and palpitation on slight exertion.

He was pale and slightly lemon colored. There was a moderate degree of glossitis. The liver could not be felt but the spleen was palpable. The urine contained a trace of albumin and urobilin. The erythrocytes numbered 1,900,000, the leukocytes 6,100, and the hemoglobin was 42 per cent. Gastric achlorhydria was present. The serum bilirubin was 3.3 mg. There was no retention of phenoltetrachlorphthalein. He was given three transfusions, with temporary improvement, but died ten months later.

SPLENIC ANEMIA (BANTI'S DISEASE)

Splenic anemia is of particular interest because of the frequent association of hepatic cirrhosis in the later stages of the disease. On the other hand, moderate enlargement of the spleen is an almost constant accompaniment of atrophic cirrhosis of the liver. In this study we have applied the term splenic anemia to a group of cases in which the characteristic features are the progressive enlargement of the spleen without known cause, the occurrence of gastric or intestinal hemorrhages, and the presence of an anemia, of varying degree, of the so-called secondary type, associated with leukopenia and often with relative lymphocytosis.[14]

14. Osler, William: On Splenic Anemia, Am. J. M. Sc. **119**:54-73, 1900; Anemia Splenica, Tr. A. Am. Phys. **17**:429-461, 1902.

TABLE 2.—*Splenic Anemia*

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm.	Jaundice	Weight of Spleen, Gm.	Ascites	Urobilin	Blood Count: Hemoglobin, %	Blood Count: Erythrocytes, Millions	Blood Count: Leukocytes	Phenolsulphonphthalein, per Cent	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Nonprotein Nitrogen	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Urea	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Uric Acid	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Creatinine	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Amino-Acid Nitrogen	Bile Pigments (Serum): Bile Index	Bile Pigments (Serum): Serum Bilirubin, Mg. per 100 Cc.	Bile Pigments (Serum): Van den Bergh Direct Reaction	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: Normal	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: 1 Hour	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: 2 Hours	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: Change	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 15 Minutes	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 1 Hour	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 2 Hours	Phenoltetrachlorphthalein: Dye in Urine, Mg.	Comment
20	5/24/24	32	♀	4	0	950	+	..	45	3.36	2,900	..	28	12	3.4	1.4	7.0	15	**3.4**	±	83	108	90	25	23	**17**	12	**1.3**	Cirrhosis observed at operation
21	9/10/23	55	♀	3	1	§	0	+	60	3.25	3,200	75	..	11	2.9	1.3	...	..	...	..	..	...	..	..	16	**14**	7	0.0	Cirrhosis
22	3/27/24	60	♂	8	1	810	0	+	68	3.91	3,800	55	28	23	3.5	1.8	7.1	15	**2.5**	0	..	...	..	..	13	**10**	6	0.4	Cirrhosis observed at operation
23	6/14/24	45	♂	0	0	630	0	..	65	3.89	6,000	..	36	28	2.9	1.6	6.6	10	1.1	±	90	120	87	**30**	11	**8**	4	0.3	Perihepatitis observed at necropsy
24	3/20/24	54	♂	6	1	730	0	0	44	3.73	6,600	40	39	..	4.5	1.5	5.6	13	1.3	0	100	**145**	124	**45**	10	**8**	5	0.0	Cirrhosis observed at necropsy
25	4/ 7/24	52	♂	0	0	§	0	..	30	2.74	3,700	..	27	12	3.9	1.2	7.4	..	**2.5**	0	104	**135**	108	**30**	..	**8**	4	0.0	Cirrhosis observed at operation
26	11/ 8/24	10	♂	..	0	630	0	..	70	4.06	5,000	..	28	14	3.0	1.2	5.0	15	**2.3**	±	..	...	..	..	10	7	5	0.5	Cirrhosis observed at necropsy
27	10/17/24	..	♂	0	0	550	0	..	33	2.95	3,600	..	34	24	3.9	1.5	6.8	8	1.0	0	..	...	..	..	8	7	4	0.3	Cirrhosis observed at necropsy
28	3/21/24	53	♂	0	0	§	++	..	73	4.90	2,200	..	..	44	...	...	...	8	...	..	127	...	..	..	9	**6**	1	...	
	10/14/24	..	..	0	0	§	+++	+	63	4.36	2,400	80	34	19	3.4	1.6	7.0	..	0.5	0	..	...	..	..	9	**6**	3	...	
29	12/24/24	37	♂	0	0	1,800	0	+	72	4.34	7,600	..	47	14	...	1.2	6.7	..	1.2	0	..	...	..	..	..	**6**	0	0.4	Cirrhosis; 19 months after splenectomy
30	3/27/24	49	♂	§	0	§	++	..	10	1.26	3,000	..	31	27	3.0	1.6	7.2	12	1.9	0	105	**143**	121	**38**	..	5	3	0.6	
31	7/ 3/23	44	♂	†	0	890	0	..	58	4.06	3,300	70	..	31	...	...	...	..	...	..	..	...	..	..	8	5	0	0.0	
32	3/ 5/25	34	♂	§	0	4,000	0	0	70	4.54	10,700	..	..	36	3.0	1.2	...	..	0.3	0	..	...	..	..	8	4	2	...	12 months after splenectomy
33	1/22/24	32	♂	0	0	800	++	..	35	2.92	3,000	50	24	17	...	...	...	..	0.9	0	..	...	..	..	8	3	0	0.0	
34	2/ 9/25	27	♂	§	0	920	0	0	77	4.89	7,600	..	..	20	2.8	1.0	...	..	0.3	0	..	...	..	..	7	3	0	0.6	12 months after splenectomy
35	4/30/25	53	♀	§	1	§	++	1	46	2.26	7,400	..	..	19	...	...	...	..	**2.1**	0	..	...	..	..	5	2	0	...	
36	2/20/24	36	♂	†	0	1,050	+	..	34	3.06	3,300	..	33	20	...	...	...	8	0.7	0	..	...	..	..	5	2	0	0.1	Cirrhosis observed at operation
37	4/ 5/24	27	♂	§	0	900	0	..	32	2.17	5,400	50	25	20	2.0	2.0	5.3	..	1.0	0	104	117	103	13	6	2	0	0.3	Cirrhosis observed at operation
38	12/ 2/24	16	♀	§	0	1,800	0	..	68	4.03	4,300	..	26	21	2.9	1.1	6.2	..	0.7	0	130	...	..	..	..	2	0	0.0	
																Splenomegaly—Gaucher Type													
39	6/18/25	50	♂	0	0	§	..	±	54	3.26	7,000	..	..	30	2.6	1.5	...	..	1.1	0	76	96	100	24	5	2	0	0.7	

Clinical evidences of hepatic disturbance are less marked. Cirrhosis, ascites and occasionally jaundice may appear in the later stages of the disease. The results of the different functional tests are shown in table 2.

CASE 4 (case 33, table 2).—A man, aged 32, had his first hematemesis in June, 1917, vomiting blood clots and fresh blood repeatedly for twelve hours. He was subsequently pale and weak; the stools were tarry, and he was in the hospital for a week. Recovery was gradual. Since then he had had five or six similar attacks, which usually followed severe exertion. Ascites followed the last hemorrhage six weeks before admission, Jan. 22, 1924.

He was pale and weak with a waxy white skin. Ascites was marked and the superficial abdominal veins were distended. After paracentesis an enlarged spleen could be felt but the liver was not palpable. The urine was normal. Blood counts showed a marked secondary type of anemia with leukopenia. The serum bilirubin was 0.9 mg. There was no retention of phenoltetrachlorphthalein.

At operation, February 27, an enlarged spleen weighing 800 Gm. was removed with great difficulty. The liver was apparently in good condition. Following the operation the ascites disappeared and recovery was uneventful.

CASE 5 (case 22, table 2).—A man, aged 60, had an attack of hematemesis in November, 1923. At that time he fainted, then vomited clots and fresh blood. The stools were tarry for several days afterward. A second attack in February, 1924, followed severe exertion.

He was subicteric in appearance when examined, March 27, 1924. He was quite obese but ascites was demonstrable. The edge of the liver extended 8 cm. below the costal margin, and the spleen was markedly enlarged. The urine contained urobilin but no bile. Moderate secondary anemia with leukopenia was present. The serum bilirubin was 2.5 mg. There was retention of phenoltetrachlorphthalein with a reading of 10 per cent.

At operation, April 15, a large spleen weighing 810 Gm. was removed. The liver was enlarged and cirrhotic in appearance. Postoperative recovery was slow and the ascites persisted for a long time. The patient was able to resume his normal activities but died, Jan. 16, 1925, following another gastric hemorrhage.

SPLENOMEGALY OF THE GAUCHER TYPE

Splenomegaly of the Gaucher type is of particular interest because it is considered as an example of primary overgrowth of the cells of the reticulo-endothelial system.[15] Mandelbaum[16] has reviewed the pathologic changes in detail and points out that infiltration of the liver is not uncommon. We are able to report studies on one case (table 2). Histologic examination of the spleen was not possible but the clinical features were rather characteristic and distinct.

CASE 6 (case 39, table 2).—A man, aged 50, was admitted to the clinic, June 18, 1925, because of splenomegaly of fourteen years' duration. In 1910 he first noted a mass in the left side which slowly increased in size. His physician made a diagnosis of splenomegaly in 1917. Since that time there had been a progressive painless enlargement of the spleen. Anemia developed slowly during this period

15. Waugh, T. R., and MacIntosh, D. S.: The Histogenesis and Nature of Gaucher's Disease, Arch. Int. Med. **33**:599-610 (May) 1924.

16. Mandelbaum, F. S.: Two Cases of Gaucher's Disease in Adults: A Study of the Histopathology, Biology and Chemical Findings, Am. J. M. Sc. **157**: 366-389 (March) 1919.

TABLE 3.—*Polycythemia Vera*

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm.	Jaundice	Spleen Enlarged	Urine: Specific Gravity	Urine: Albumin	Urine: Urobilin	Blood Count: Hemoglobin, %	Blood Count: Erythrocytes, Millions	Blood Count: Leukocytes	Whole Blood Volume, Cc. for Each Kg.	Phenolsulphonphthalein, per Cent	Blood Nitrogen Partition, Mg. for Each 100 Cc.: Nonprotein Nitrogen	Urea	Uric Acid	Creatinine	Amino-Acid Nitrogen	Bile Pigments (Serum): Serum Bilirubin, Mg. per 100 Cc.	Van den Bergh Direct Reaction	Fructose Tolerance: Blood Sugar, Mg. for Each 100 Cc.: Normal	1 Hour	2 Hours	Change	Phenoltetrachlorphthalein: Dye in Serum, per Cent: 15 Minutes	1 Hour	2 Hours	Dye in Urine, Mg.	Comment
40	6/19/25	31	♀	0	0	†	1.020	0	0	141	6.89	9,500	167	40	15	11	3.4	1.4	11.0	1.5	0	105	...	...	..	12	**5**	0	0.6	Before treatment
	7/ 7/25	..	..	3	1	§	1.019	2	+	63	4.20	16,900	104	65	51	69	2.5	1.5	....	**5.7**	0	84	109	87	25	10	**6**	2	...	During treatment with phenylhydrazine
41	7/15/24	44	♂	3	0	§	1.026	2	0	170	7.41	8,700	165	40	53	47	4.9	1.4	11.3	1.6	0	107	122	108	15	8	5	0	0.6	
42	4/17/25	56	♂	0	0	0	1.018	2	0	214	8.36	6,700	190	55	49	45	2.9	1.8	8.9	0.9	0	75	98	92	23	8	3	0	...	Before treatment
	5/ 1/25	..	..	0	±	†	1.015	1	+	150	4.97	15,000	136	35	62	52	4.0	2.2	11.3	**2.4**	0	81	97	83	16	3	1	0	...	During treatment with phenylhydrazine
43	12/15/24	62	♂	1	0	†	1.015	1	0	163	7.85	14,000	183	40	..	16	2.9	1.6	9.2	1.7	0	...	...	...	..	8	3	0	0.0	Before treatment
	2/ 5/25	..	..	§	0	†	1.010	1	+	90	2.51	18,500	116	40	..	45	...	1.8	8.0	**2.5**	0	...	...	...	..	3	1	0	0.0	During treatment
44	4/14/24	50	♂	5	0	†	1.006	2	..	150	6.58	24,000	172	75	45	33	6.4	1.7	11.9	**2.9**	0	...	...	...	..	7	3	1	0.5	Gout
45	2/ 9/25	58	♂	0	±	†	1.024	0	..	138	5.93	9,900	116	50	..	26	2.8	2.2	14.3	1.7	0	...	...	...	..	5	1	0	0.9	
																														Myelogenous Leukemia
46	4/23/25	22	♂	4	0	§	1.018	1	..	36	3.37	459,000	...	..	69	28	5.1	1.8	11.3	0.1	0	76	86	100	24	7	3	1	0.3	
47	4/20/25	22		†	0	§	1.023	1	..	40	3.11	360,000	...	..	75	26	2.9	1.5	21.2	0.1	0	...	...	...	..	8	2	0	0.3	
48	4/21/25	50	♀	0	0	§	1.017	1	..	70	4.13	199,000	...	..	63	22	3.7	1.4	9.4	0.3	0	86	95	89	9	6	2	1	0.0	
49	5/ 5/25	57	♀	0	0	†	1.027	0	..	46	3.35	85,000	...	..	37	29	3.7	1.0	7.3	0.1	0	114	98	111	16	7	3	0	0.5	After radium treatment
50	8/26/25	45	♀	0	0	§	1.026	0	..	47	3.50	51,000	...	..	36	31	2.8	...	7.1	0.1	0	...	...	...	..	6	2	0	...	After radium treatment
																														Lymphatic Leukemia
51	6/12/25	53	♀	†	0	0	1.010	1	..	22	2.21	227,400	...	..	42	24	3.0	1.9	7.9	0.1	0	100	106	111	11	7	5	2	...	
52	7/12/25	37	♂	0	0	†	1.020	0	..	56	3.99	116,000	...	..	..	59	1.2	4.5	6.0	0.4	0	82	100	94	18	7	3	0	0.0	
53	6/10/25	53	♀	0	0	0	1.030	0	..	59	4.06	75,000	...	..	33	33	3.5	1.3	6.9	0.4	0	111	**142**	118	**31**	7	3	1	...	
54	6/ 5/25	61	♂	0	0	†	1.019	0	..	70	4.51	6,800	...	..	34	33	2.2	2.0	7.3	0.4	0	81	93	83	12	2	1	0	0.0	After radium treatment

but apart from that and the fulness of the abdomen, he felt well, and he was able to continue his usual work. One sister was reported to have had a large spleen.

The patient appeared moderately anemic, with characteristic pigmentation of the face and neck and pinguecula of the cornea. The spleen was very large, practically filling the abdomen. Moderate anemia of secondary type was present. The erythrocytes numbered 3,260,000, the leukocytes 7,000, and the hemoglobin was 54 per cent. The differential leukocyte count was normal. The serum bilirubin was 1.1 mg., and there was no retention of phenoltetrachlorphthalein.

POLYCYTHEMIA VERA (ERYTHREMIA)

True polycythemia is the converse of anemia in that it is characterized by a persistent increase in the red blood corpuscles with resultant plethora. The clinical features of the condition have recently been discussed by Fitz.[17] Brown and Giffin[18] have followed the changes in the total blood volume and particularly stress the vascular readjustments to the increased volume of the circulating blood. We are able to report additional studies on some of these cases. These are of particular interest in that phenylhydrazine was used therapeutically in four. We are able, therefore, to compare the changes in true hemolytic icterus with those in the artificial hemolytic icterus produced by this means.

CASE 7 (case 40, table 3).—A woman, aged 31, came to the clinic, June 15, 1925, because of stomach trouble of six years' duration. It began with pain in the epigastrium and along the left costal margin, accompanied by nausea but not by vomiting. The attacks became more frequent and were associated with severe headaches which recurred every two weeks. In 1922, a tumor in the left side of the abdomen was discovered by the family physician. He removed the appendix and gallbladder but did not disturb the tumor. Since then the patient has been worse, with frequent attacks of headache, and pain in the left upper quadrant of the abdomen, accompanied by nausea and vomiting.

The patient was asthenic and weighed but 108 pounds (49 Kg.), having lost 25 pounds (11.3 Kg.) in about two years. The face and hands were a full dusky red, the lips bluish, and the nails cyanotic. Ophthalmoscopic examination showed the retinal veins to be full and congested. The heart was not enlarged and the sounds were clear. The spleen was enlarged and extended 3 cm. below the costal margin. The liver was not palpable. There was a marked polycythemia, the erythrocytes numbering 6,890,000, while the blood volume was 176 cc. for each kilogram of body weight. The blood urea was 11 mg. The serum bilirubin was 1.5 mg., and there was no retention of phenoltetrachlorphthalein.

The patient was then given phenylhydrazine by mouth in a dosage of 0.3 Gm. daily for a period of twelve days. In all 3.5 Gm. of the drug was given. During this period there was marked destruction of red blood cells. The cyanosis disappeared. The liver enlarged until the edge was palpable 3 cm. below the costal margin. The spleen reached a level 6 cm. below the costal margin. The erythrocyte count decreased to 4,200,000, and the whole blood volume to 104 cc. for each kilogram of body weight. The serum bilirubin increased to 7.7 mg., and slight jaundice appeared (fig. 1). Urobilin and urobilinogen appeared in the urine. The blood urea increased to 69 mg. and albumin and red blood cells appeared in the urine. The phenolsulphonphthalein excretion, however, was 65 per cent at this time. There was no change in the excretion of phenoltetrachlorphthalein. The

17. Fitz, Reginald: Polycythemia, Oxford Med. **2**:763-778, 1920.

18. Brown, G. E., and Giffin, H. Z.: Studies of the Vascular Changes in Cases of Polycythemia Vera, Am. J. M. Sc. **171**:157-168, 1926.

administration of the phenylhydrazine was stopped. Thereafter, the jaundice rapidly disappeared and the liver and spleen returned to their original dimensions. The erythrocyte count fell to 2,500,000, and the blood volume to 89 cc. for each kilogram of body weight, and then became stationary. The urine again became normal. The blood urea was 24 mg. The serum bilirubin returned to normal. The patient was dismissed, July 23, with complete symptomatic relief.

LEUKEMIA

The usual case of leukemia is characterized by a marked increase in the leukocytes of the blood associated with hyperplasia of the leukoblastic tissues. In cases of the myelogenous type the spleen may be very greatly enlarged, while the lymphatic form is not characterized by appreciable splenomegaly but by lymphglandular enlargement. Enlargement of the liver is common and is usually associated with infiltration by the leukemic elements from the blood. The effect of such changes on the functional efficiency of the liver is of extreme interest. The findings in a series of characteristic cases are shown in table 3.

CASE 8 (case 46, table 3).—A man, aged 28, was admitted to the clinic, April 21, 1925, because of increasing weakness over a period of three months. Loss of strength and energy had been marked. A mass under the left costal margin had been noted two months before admission. There was no gastro-intestinal disturbance.

The patient was pale and thin, weighing but 115 pounds (52.1 Kg.). The superficial lymph nodes in the groin were enlarged. The liver extended 4 cm. below the costal margin. Its surface was smooth and the edge rounded. The spleen was tremendously enlarged and filled the whole left side of the abdomen. Blood smears showed myelogenous leukemia with a leukocyte count of 459,000. Moderate anemia of secondary type was present. The serum bilirubin was 0.1 mg. There was no retention of phenoltetrachlorphthalein. Following the application of radium over the spleen the condition improved markedly.

CASE 9 (case 51, table 3).—A woman, aged 53, first noted a small nodule in the right submaxillary region in 1924. This slowly increased in size at first, but in January, 1925, the growth became more rapid and other tumors appeared, first in the cervical, and then in the axillary and inguinal regions. Two months before admission, June 4, 1925, asthenia and weakness became marked.

There was a marked general enlargement of lymph nodes. The right cervical region in particular was occupied by a mass of large confluent nodules of varying consistency. There was a mass in the right axilla. The liver edge was just palpable but the spleen could not be felt. The erythrocytes numbered 2,210,000, and the hemoglobin was 22 per cent. The leukocytes numbered 227,400, and a differential count showed the presence of 98 per cent of lymphocytes. The serum bilirubin was 0.1 mg. There was no retention of phenoltetrachlorphthalein.

INDIVIDUAL TESTS

Fructose Tolerance.—The fructose tolerance was studied in three cases of hemolytic jaundice with a normal response in all. No disturbance was noted in the five cases of pernicious anemia in which this test was made. This is in accord with the results of Kahn and Barsky,[19]

19. Kahn, Max; and Barsky, Joseph: Studies of the Chemistry of Pernicious Anemia, Arch. Int. Med. **23**:334-345 (March) 1919.

who found the Bauer and Strauss tests negative in two cases of pernicious anemia. Similar results were secured by Hetényi.[20]

Six cases of splenic anemia were studied. A positive fructose test was obtained in three and a suggestive test in one other. Goebel [21] has reported positive fructose and galactose tests in two cases, and considers them evidence of hepatic cirrhosis. The extent of change in the fructose tolerance tests observed in our cases did not uniformly agree with the extent of the changes visible in the liver at the time of operation. In the cases of cirrhosis with ascites of the Laënnec type positive fructose tolerance tests were irregularly obtained.[22] In splenic anemia, then, we do not feel that a negative test can be used to exclude the presence of changes in the liver.

Negative tests were obtained in the cases of polycythemia. This was so even during the course of treatment with phenylhydrazine. Bodansky [23] has reported a marked decrease in the sugar tolerance of dogs as a result of toxic doses of phenylhydrazine. The dose, however, was such as to produce toxic lesions in the liver.

Tests were made in seven cases of leukemia. A reduction in the fructose tolerance was observed in one. A normal response was obtained in the case of Gaucher's splenomegaly.

There was no disturbance in the fasting blood sugar level in any of the cases studied. Mann and Magath [24] have emphasized the rôle of the liver in carbohydrate metabolism. They have likewise emphasized the relatively small proportion of the whole organ that is needed to maintain this activity. We have previously pointed out [25] that the most striking changes in sugar tolerance are those produced experimentally by poisons that cause direct toxic injury to the organ as a whole. Iron may be deposited in the liver in large amounts in cases of pernicous anemia or hemolytic icterus, and the liver may be enlarged as the result

20. Hetényi, Géza: Die Funktionsprüfung der Leber mittels gleichzeitiger Bilirubinbestimmungen im Blutserum und in der Galle, Ztschr. f. klin. Med. **95**:469-490 (Nov. 30) 1922; abstr. J. A. M. A. **80**:517 (Feb. 17) 1923; Die Leberfunktion und ihre Bedeutung in der perniziösen Anämie, Wien. klin. Wchnschr. **37**:1138-1140 (Oct. 30) 1924.

21. Goebel, F.: Banti'sche Krankheit und Leberfunktion zur Abgrenzung gegen die Leber cirrhose, Deutsches Arch. f. klin. Med. **146**:202-211 (Feb.) 1925.

22. Greene, C. H.; McVicar, C. S., and Rowntree, L. G.: Diseases of the Liver: VI, The Functional Changes Accompanying Cirrhosis, to be published.

23. Bodansky, Meyer: The Action of Hydrazine and Some of Its Derivatives in Producing Liver Injury as Measured by the Effect on Levulose Tolerance, J. Biol. Chem. **58**:799-811 (Jan.) 1924.

24. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: II, The Effect of the Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73-84 (July) 1922.

25. Greene, C. H.; McVicar, C. S.; Rowntree, L. G., and Walters, Waltman: Diseases of the Liver: IV, Functional Tests in Carcinoma of the Liver and Biliary Tract, Arch. Int. Med. **36**:542-560 (Oct.) 1925.

of infiltration with fat in cases of pernicious anemia or by leukoblastic cells in cases of leukemia. These changes may be striking from the histologic point of view but the functional changes in the cases studied by us were apparently not comparable in magnitude. We have not been able to show clinically significant changes by means of the fructose tolerance test.

Nitrogen Partition of the Blood.—Kahn and Barsky [19] found no particular change in the nitrogen partition of the blood in cases of pernicious anemia. Gettler and Lindeman,[26] on the other hand, found the nonprotein nitrogen, urea, uric acid and creatinine to be slightly increased. This increase, which was not marked, they attributed to decreased volume of the blood. Keith,[27] however, has found that in

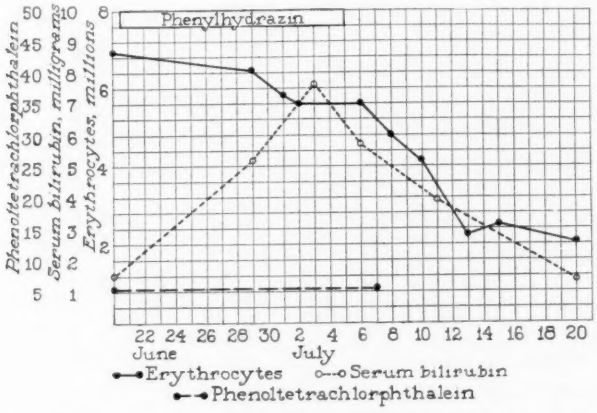
Phenylhydrazin
Phenoltetrachlorphthalein
Serum bilirubin, milligrams
Erythrocytes, millions
50 45 40 35 30 25 20 15 10 5
10 9 8 7 6 5 4 3 2 1
8 6 4 2
22 24 26 28 30 2 4 6 8 10 12 14 16 18 20
June
July
Erythrocytes
Serum bilirubin
Phenoltetrachlorphthalein

Fig. 1.—Changes in serum bilirubin, phenoltetrachlorphthalein and erythrocytes in case 7 during artificial hemolytic crisis produced by therapeutic use of phenylhydrazine.

cases of pernicious anemia the whole blood volume is normal while the plasma volume may be markedly increased in consequence of the lowered erythrocyte content.

We found no characteristic changes from the normal in the nonprotein nitrogenous constituents of the blood in cases of pernicious anemia, hemolytic jaundice or splenic anemia. The blood urea and total nonprotein nitrogen were increased following a hemolytic crisis in one patient with pernicious anemia (case 2). The urinary output of this patient was adequate and the blood urea returned toward normal as the jaundice disappeared. Similar changes were observed in the

26. Gettler, A. O., and Lindeman, E.: Blood Chemistry of Pernicious Anemia, Arch. Int. Med. **26**:453-458 (Oct.) 1920.

27. Keith, N. M.: The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am. J. M. Sc. **165**:174-184 (Feb.) 1923.

cases of polycythemia vera during treatment with phenylhydrazine. The changes in both instances were apparently determined by an increased destruction of erythrocytes and a flooding of the organism with the products of protein catabolism. An analogy may well be drawn to the effect of a meat meal, or to the effect of a diet high in protein.

The most striking change found by Gettler and Lindeman in cases of pernicious anemia was a fourfold increase in the amino-acid nitrogen. The values for the amino-acid nitrogen in cases of pernicious anemia, hemolytic icterus and splenic anemia obtained by the Folin technic came within the normal limits suggested by Greene, Sandiford and Ross.[28] In cases of leukemia, on the other hand, as pointed out by Okada and Hayashi,[29] and by Sandiford, Boothby and Giffin,[30] there is a striking increase in the amino-acid nitrogen. This is particularly true in cases of myelogenous leukemia. We found similar changes in cases of polycythemia vera, although they were less striking than those found in cases of leukemia.

Martin, Denis and Aldrich[31] found evidence of an increase in the rest nitrogen in the blood in cases of leukemia, and suggested that this increase might be due to amino-acids. We have found a similar increase in the rest nitrogen of the whole blood. This is most marked in cases of myelogenous leukemia and least in cases of polycythemia vera. The changes in leukemia correspond roughly to the increase in the leukocyte count. The amino-acids are increased under these conditions, but the increase is not sufficient to account for the whole of the changes in the rest nitrogen. The unknown substance apparently is a product of cellular activity since it is greater in the corpuscles than in the plasma or serum and is present in largest amounts in the leukocytes. Grafe[32] especially has emphasized the metabolic activity of the white corpuscles in cases of leukemia. The increase in the rest nitrogen of the blood is perhaps additional evidence on this point.

Serum Bilirubin.—The yellow color of the serum in cases of pernicious anemia was pointed out by Naegeli,[33] and has since been

28. Greene, C. H.; Sandiford, Kathleen; and Ross, Helen: The Amino-Acid Content of the Blood in Normal and Pathologic Conditions, J. Biol. Chem. **58**:845-857 (Jan.) 1924.

29. Okada, S., and Hayashi, T.: Studies on the Amino-Acid Nitrogen Content of the Blood, J. Biol. Chem. **51**:121-133 (March) 1922.

30. Sandiford, Kathleen; Boothby, W. M., and Giffin, H. Z.: The Amino-Acid Nitrogen in the Blood and Its Possible Relation to the Elevation of the Metabolism in Myelaginous Leukemia, J. Biol. Chem. **55**:23-24, 1923.

31. Martin, C. I.; Denis, W., and Aldrich, Martha: A Chemical Study of Blood Changes Following Roentgen-Ray Treatment of Leukemia, Am. J. M. Sc. **160**:223-233 (Aug.) 1920.

32. Grafe, E.: Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, Deutsches Arch. f. klin. Med. **102**:406-430, 1911.

33. Naegeli, Otto: Blutkrankheiten und Blutdiagnostik, Ed. 3, Berlin, W. de Gruyter and Co., 1919.

emphasized by Brockbank,[34] Riggs,[35] Gram [36] and others. Blankenhorn,[37] by means of the Gmelin test, was able to demonstrate the presence of bilirubin in the serum. More exact studies dealing with determination of the precise quantities of bilirubin present have been made by van den Bergh,[2] Lepehne,[3] and Broun, Ames, Warren and Peabody.[38] The last mentioned, especially, have followed the changes in the plasma bilirubin over a period of time and report the close relationship between an increase in this pigment and the clinical exacerbations of the disease.

The cases of pernicious anemia studied in the present series show similar changes. In the majority the amount of serum bilirubin was at the upper limit of the normal, or slightly increased beyond these limits, the amounts varying from 1.4 to 5 mg. for each hundred cubic centimeters of blood (fig. 2). In none of these cases was a true "prompt"

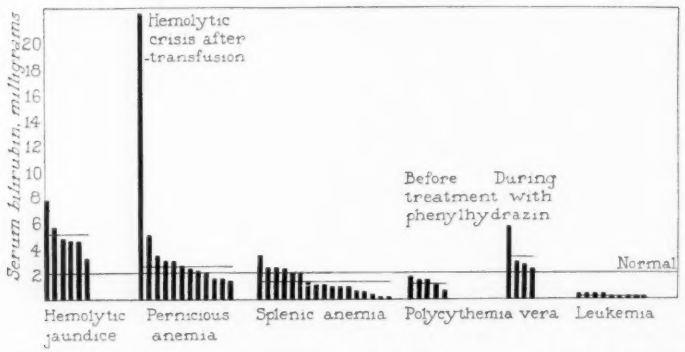

Fig. 2.—Variation in serum bilirubin in different diseases of the hematopoietic system; the maximal normal level is indicated, and in each group the average value is shown by the horizontal line.

direct van den Bergh reaction obtained. The reaction was either "indirect" or "delayed." Differences in the methods of interpreting the results of this test will explain the higher proportion of "delayed" reactions reported by Broun, Ames, Warren and Peabody.[38] In one case (case 2) following a hemolytic crisis, frank jaundice developed. The

34. Brockbank, E. M.: The Blood Serum in Pernicious Anemia, with Notes on the Nature of the Disease and Its Treatment, Brit. M. J. **2**:124-126 (July 22) 1922.

35. Riggs, C. E.: Preliminary Note: A Study of the Nervous Syndrome and the Blood Serum in Pernicious Anemia as an Aid in Diagnosis Before Recognizable Changes Are Apparent, Minnesota Med. **7**:484-495 (July) 1924.

36. Gram, H. C.: Meulengracht's Plasma Color Determination, Ugesk. f. Læger **82**:1137-1139 (Sept. 2) 1920.

37. Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, Arch. Int. Med. **19**:344-353 (March) 1917.

38. Broun, G. O.; Ames, O.; Warren, S., and Peabody, F. W.: Blood Pigments in Pernicious Anemia, J. Clin. Invest. **1**:295-316, 1925.

serum bilirubin was increased to 26.2 mg. for each hundred cubic centimeters of blood and a "prompt" direct van den Bergh reaction was obtained.

The serum bilirubin was uniformly increased in the cases of hemolytic icterus, varying from 3.3 to 7.7 mg. The van den Bergh reaction was "indirect" in the majority of these cases although a "delayed" reaction was obtained in one and a "direct" reaction in case 1 (table 1), showing the most marked icterus. Biliary obstruction by associated gallstones may serve to explain the "direct" reaction in such cases.

In five of the cases of splenic anemia there was slight bilirubinemia; normal values were obtained in the others. There seemed to be no direct relation between the amount of serum bilirubin and the degree of the anemia in these patients.

Normal values for the serum bilirubin were obtained in five of the cases of polycythemia vera. Three of these cases were studied during the therapeutic administration of phenylhydrazine. In each case bilirubinemia, with an "indirect" van den Bergh reaction, resulted. In the cases of leukemia, on the other hand, the serum bilirubin was reduced in quantity and low values were the rule.

The bilirubinemia and jaundice observed in cases of hemolytic icterus, pernicious anemia, or following the therapeutic use of phenylhydrazine, is hemolytic in origin. It is therefore primarily a measure of the intensity of the hemolytic process rather than of disturbance in the functional activity of the liver. We recognize the possibility of an alteration in the hepatic threshold for the excretion of pigment which may be in part responsible for the bilirubinemia in these cases, but such an alteration, if present, should be considered as an accompaniment of the hemolytic process rather than evidence of direct hepatic damage.

Phenoltetrachlorphthalein.—The phenoltetrachlorphthalein test was negative in nine of the twelve cases of pernicious anemia studied (fig. 3). Marked retention of dye was present in one case (case 2) which was observed during the peak of a hemolytic crisis. The dye retention apparently should be related to the marked bilirubinemia for a slight degree of retention of dye was observed in three out of seven cases of hemolytic jaundice. Bilirubinemia was the most marked (4.4 to 7.7 mg.) in these cases. The degree of retention observed in these cases was slight and contrasts with the observations previously reported in cases of obstructive jaundice in which the degree of retention of dye more closely corresponds to the degree of retention of bile and bilirubinemia.

In the cases of splenic anemia a retention of phenoltetrachlorphthalein was observed in eleven of nineteen cases studied. The determination of the extent of cirrhotic changes in the liver, wholly on the basis of the appearance of that organ at the time of operation, is manifestly impossible. Nevertheless, it is noteworthy that in those cases in which the

surgeon reported the most marked cirrhotic changes there was considerable retention of dye, while no retention was present in the cases in which the liver appeared to be normal. Retention of phenoltetrachlorphthalein in such cases is apparently an index to the extent of the changes in the liver. Four cases in the series showed a slight increase in the serum bilirubin above the normal level. In each instance this accompanied distinct retention of dye.

A normal response to the phenoltetrachlorphthalein test was obtained in the cases of polycythemia vera and leukemia.

COMMENT

These observations are of particular interest in the study of the relation between the serum bilirubin and the rate of blood destruction. That hemolytic jaundice is associated with an increased rate of blood destruc-

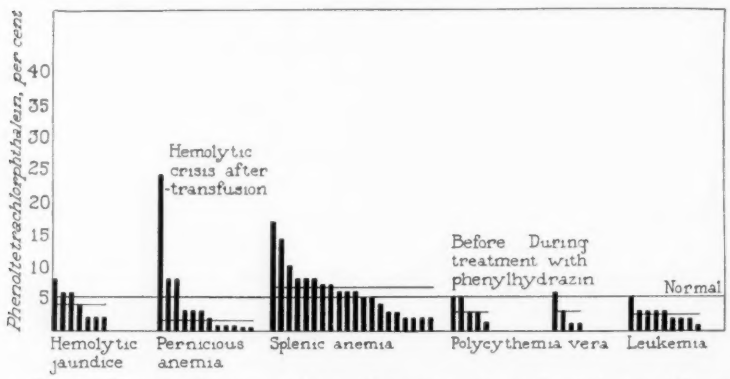

Fig. 3.—Variation in degree of phenoltetrachlorphthalein retention in different diseases of the hematopoietic system. The maximal normal level is indicated, and in each group the average value is shown by the horizontal line.

tion has long been recognized. That similar factors are active in pernicious anemia is increasingly evident.

The importance of the rate of blood destruction in maintaining the serum bilirubin is shown in the cases in which phenylhydrazine was given to reduce the number of erythrocytes. In these the hemolytic action of the drug was signaled by an increase in the serum bilirubin and by the appearance of hematin in the urine, and it was possible to follow the curve of hemolysis in this way. The similarity between the changes in these cases and in case 2 is striking. In the latter, transfusion was followed by marked clinical evidence of hemolysis with jaundice and the appearance of bile in the urine. At the same time the serum bilirubin and the blood urea increased. The changes were transitory in nature and disappeared as soon as the products of the destruction of the erythrocytes were excreted.

The locus of origin of the bilirubin in cases of pernicious anemia and hemolytic icterus is important. The value of splenectomy in combating the effects of the latter disease is strikingly suggestive. Van den Bergh and Snapper [39] have examined the blood from the splenic artery and vein in a few cases and report the finding of more bilirubin in the venous blood than in the arterial. Rosenthal [40] and Lepehne [3] studied single cases of hemolytic jaundice and splenic anemia and were unable to confirm this finding. Rich and Reinhoff [41] more recently have reported a study of the serum bilirubin in a series of ten cases. In four the blood from the splenic vein contained more bilirubin than the control blood. Similar results have been reported by Kaznelson.[42] Our results shown in table 4 confirm this finding.

These observations strikingly confirm the clinical impressions concerning the activity of the spleen in destroying erythrocytes. They further emphasize the fact that the increase in the serum bilirubin in

TABLE 4.—*Origin of Bilirubin in Hemolytic Jaundice and Splenic Anemia*

Case	Diagnosis	Bilirubin in Blood from Splenic Artery, Mg. for Each 100 Cc.	Bilirubin in Blood from Splenic Vein, Mg. for Each 100 Cc.	Difference, Mg. for Each 100 Cc.
1	Hemolytic jaundice	3.6	4.8	1.2
2	Splenic anemia	0.4	1.0	0.6
3	Splenic anemia	0.6	1.1	0.5

these cases is an index to the intensity of the hemolytic process and not to a pathologic disturbance in the functional activity of the liver. At the same time they should not be interpreted as evidence of an exclusive function of the spleen, for Mann and his co-workers have shown that jaundice will develop in dogs after the complete removal of the liver, spleen and other abdominal viscera, although bilirubinemia appears more slowly than in animals with an intact spleen. Recently Mann, Sheard, Bollman and Baldes [43] have been able to show by spectrophotometric methods that minute traces of bilirubin are normally and constantly

39. Van den Bergh, A. A. H., and Snapper, I.: Ueber anhepatische Gallenfarbstoffbildung, Berl. klin. Wchnschr. **21**:1081-1086, 1915.

40. Rosenthal, F.: Untersuchungen zur Chemie des Blutes beim hämolytischen Ikterus mit besonderer Berücksichtigung der Lipoide, Deutesches Arch. f. klin. Med. **132**:129-178 (May) 1920.

41. Rich, A. R., and Rienhoff, W. F., Jr.: The Bile Pigment Content of the Splenic Vein, Bull. Johns Hopkins Hosp. **36**:431-436 (June) 1925.

42. Kaznelson, P.: Beitrag zur Entstehung des hämolytischen Ikterus, Wien. Arch. f. inn. Med. **1**:563-574 (Aug.) 1920.

43. Mann, F. C.; Sheard, Charles; and Bollman, J. L.: Studies on the Physiology of the Liver: XI, The Extrahepatic Formation of Bilirubin, Am. J. Physiol. **74**:49-60 (Sept.) 1925. Mann, F. C.; Sheard, Charles; Bollman, J. L., and Baldes, E. J.: The Site of the Formation of Bilirubin, Am. J. Physiol. **74**:497-510 (Nov.) 1925.

present in dogs' blood. These traces apparently arise chiefly in the bone marrow and spleen. Broun and his associates [38] have especially emphasized the relation in pernicious anemia between the amount of serum bilirubin and the apparent activity of the disease. This phenomenon they interpret as evidence for the view that pernicious anemia is associated with increased destruction of blood. We are in entire accord with this view and wish again to emphasize the value of the estimation of the serum bilirubin in distinguishing between the primary or hemolytic anemias and certain secondary anemias, especially splenic anemia, or that associated with carcinoma.

The accumulation of an iron containing pigment in the liver in pernicious anemia is well known.[44] Stieglitz [45] has emphasized the infiltration of the kidney with this pigment and suggested that disturbance in renal function may result from it. We have not been able to demonstrate a definite disturbance in the functional activity of the liver although marked morphologic changes have been described in consequence of the infiltration with pigment or fat. Bilirubinemia was present but this probably was the direct result of the hemolytic process. Proof that it is secondary to the changes in the liver is lacking.

SUMMARY

Functional disturbances in the liver are apparently not sufficiently great to be of clinical significance in most diseases of the hematopoietic system, hemolytic jaundice, pernicious anemia, polycythemia, leukemia or of splenomegaly of the Gaucher type. The greater number of tests for hepatic function studied did not show significant changes from the normal. Infiltration of the liver by iron containing pigments, fat or leukoblastic cells, has been described in these different conditions but if functional disturbances are produced by this infiltration they were not such in kind or degree as to be demonstrable in these cases by the methods studied.

An increase in serum bilirubin is of value in the differential diagnosis between hemolytic anemias and the ordinary secondary types. In cases of hemolytic icterus and pernicious anemia, changes in the serum bilirubin serve accurately to indicate changes in the severity of the hemolytic process. The serum bilirubin is equally of value in following the course of a hemolytic crisis after transfusion, or the artificial hemolytic crisis produced by the therapeutic use of phenylhydrazine. The serum bilirubin in these instances is an index to the severity of the hemolytic process rather than to disturbances in the liver.

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44. MacCallum, W. G.: Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1916.

45. Stieglitz, E. J.: Disturbances of Renal Function in Pernicious Anemia, Arch. Int. Med. **33**:58-70 (Jan.) 1924.

The "indirect" diazoreaction when associated with an increase in the serum bilirubin is characteristic of an icterus of hemolytic origin, and is of diagnostic value. The frequent association of gallstones with hemolytic jaundice will serve to account for the occasional "direct" diazoreactions obtained in the latter condition.

In cases of splenic anemia particularly the phenoltetrachlorphthalein test shows changes that may apparently be related to the severity of the cirrhotic changes in the liver. Under these conditions the test would seem to be of some diagnostic and prognostic value.

In cases of myelogenous leukemia, and to a lesser extent in those of lymphatic leukemia and polycythemia vera, there is a disturbance in the nonprotein nitrogen partition in the whole blood. This is characterized by an increase in the amino-acids and undetermined nitrogen fractions with a consequent increase in the total nonprotein nitrogen. These changes are perhaps to be related to the metabolic activity of the cells themselves and especially that of the leukocytes rather than to any general metabolic disturbance.

PERSISTENT PREMATURE CONTRACTIONS

A CLINICAL STUDY *

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This article is a report of the results obtained in a clinical study of the premature contraction, with particular regard to its reaction to the drugs most commonly used in the treatment and study of heart disease.

There are in the literature many references to the response of the premature contraction to drugs, as appendixes to studies of cardiac arrhythmias in which attention is given particularly to auricular fibrillation and flutter. This is especially the case in the recent work on the action of quinidine.

Edens and Huber [1] and Wenckebach [2] reported the action of digitalis on the premature contraction, but recorded impressions rather than the results of carefully controlled experiments.

The arrhythmia does not easily lend itself to careful study because of its inconstancy. Patients showing frequent premature contractions in great numbers over long periods of time are not often seen at the hospital. Approximately, one of every five patients with premature contractions in the cardiac clinic maintained them over sufficiently long periods of time while under observation there to make them suitable for purposes of study.

Considerable care was utilized in the selection of patients for this study. Patients were not considered as suitable unless there was no spontaneous disappearance of the premature contractions over a period of at least one month while under observation in the clinic.

METHOD

Each person selected for the study was admitted to the hospital and put to bed. At least three five minute electrocardiograms on a preferred lead, usually Lead II (this depended on the clarity of the

* From the third medical (New York University) division and adult cardiac clinic of Bellevue Hospital and the department of pharmacology, Cornell University Medical College.

1. Edens, E., and Huber, J. E.: Ueber Digitalisbigemenie, Deutsches Arch. f. klin. Med. **118**:476, 1916. Edens, E.: Ueberdigitaliswirking, Deutsches Arch. f. klin. Med. **104**:512, 1911.

2. Wenckebach, K. F.: The Effects of Digitalis on the Human Heart, Brit. M. J. **2**:1600, 1910.

curve), were taken daily, approximately at 9 a. m., 1 p. m. and 5 p. m. These electrocardiograms were taken on bromide paper and yielded strips averaging about 30 feet long.

In the earlier cases five readings a day were taken, but later it was found that three were adequate, because the average of three readings a day differed little from the average of five readings a day.

Whenever the electrocardiograph was not available, clinical readings were taken. These were obtained by the observer with the stethoscope at the apex and his free hand recording with paper and pencil the number of normal beats between each premature contraction; thus, 3/2/6/5/4/2//1/2/, etc., the numerals representing the normal beats, the vertical lines, the premature contractions. If more than one occurred in succession the strokes were set down accordingly.

From each record the following facts were ascertained:

1. The total number of consecutive beats.

2. The total number of premature contractions.

3. The division of the premature contractions into right and left ventricular and auricular.

4. The constancy of the "focus."

5. The heart rate.

6. The pattern of the premature contractions, i. e., the number of normal beats between premature contractions.

The total number of beats, the total number of premature contractions and the heart rate were then used to determine the average number of premature contractions per minute over the period by simple proportion.

The results of the foregoing calculations made from the readings of each day were averaged and the figure obtained used as the average number of premature contractions per minute the individual had that day. Furthermore, where studies were made of drugs with transient effects, electrocardiograms were taken either continuously during the study, or every five minutes, hour, two hours, etc., as the case demanded. No medication was administered during the first seven days, the minimal control period, to fourteen days, the maximal control period in the hospital.

As already stated, these patients had been without medication for one month in the clinic prior to admission into the hospital. It was in view of the known inconstancy of the arrhythmia that this elaborate procedure was thought necessary.

From the accompanying table (table 1) of the patients used for the study, it may be seen that the group of twelve cases studied include patients of both sexes between the ages of 23 and 66 with practically

every common variety of heart disease, viz., rheumatic, syphilitic, arteriosclerotic, with and without hypertension, and those of "unknown" etiology with or without other evidence of heart disease. Such a variety of cases incidentally offered an opportunity to compare the response to various drugs, of the premature contraction occurring in the different types of heart disease.

TABLE 1.—*The Cases Studied as to Etiology, Anatomy and Function* *

Case	Sex†	Age	Predominant Type of Premature Contractions‡	Diagnosis	Condition			Further Comment	Result		
					At Time of Study	During Study	End of Study		Epinephrine	Quinine	Digitalis
1	♂	53	A	Syphilitic aortic dilatation and regurgitation	IIA	IIA	IIA	.....	+ + +	— — —	— — —
2	♀	48	A	Unknown; enlarged heart hypertension	IIB	IIB	IIB	.....	+ + +	— —	....
3	♂	66	A	Arteriosclerosis and enlarged heart; hypertension	IIA	IIA	IIA	Died suddenly, cerebral hemorrhage	+ + +	— —	....
4	♀	38	A	Rheumatic mitral stenosis and insufficiency	IIA	IIA	IIA	.....	+ + +	— —	— —
5	♂	26	V	Unknown; no other evidence of heart disease	I	I	I	.....	+ + +	—	— — —
6	♀	23	V	Unknown; no other evidence of heart disease	I	I	I	.....	+ + +	—	....
7	♂	46	V	Unknown; double mitral and aortic disease	IIA	IIA	IIA	.....	+ + +	—	—?
8	♂	56	V	Arteriosclerosis; enlarged heart; hypertension	IIA	IIA	IIA	.....	+ + +	—	— — —
9	♂	46	V	Unknown; enlarged heart	III	IIB	IIA	Back in hospital 1 week later	+ + +	—	—?
10	♂	55	V	Arteriosclerosis; enlarged heart	III	IIB	IIB	.....	+ + +	—	— —
11	♀	41	V	Arteriosclerosis; aortic insufficiency	III	III	III	Died three weeks later	+ + +	— — —	....
12	♂	46	V	Rheumatism; mitral stenosis and insufficiency; intraventricular block	III	III	III	Died	+ + +	—	—

* The variations of age and diagnoses should be noted.
† In this table, ♂ indicates male; ♀, female.
‡ A indicates auricular premature contractions; V, ventricular premature contractions.

All patients had clinical cardiac enlargement except two in whom ventricular premature contractions were the only evidence of heart dysfunction. One of the latter had had syphilis with intensive treatment some years before.

In table 1, the last three columns represent the relative degree of response of each patient to epinephrine, quinine and digitalis. The plus signs represent increase in the number of premature contractions occurring per minute; the minus signs represent diminution in the number of premature contractions occurring under the influence of the drug.

THE TYPE OF PREMATURE CONTRACTION

In any single case one type of premature contraction predominated. Thus, in four patients the premature contractions were predominantly auricular, in eight predominantly ventricular, and of the latter, in three predominantly right ventricular and in five left ventricular in origin. While one type predominated in each case, almost all at some time during observation showed auricular premature contractions if they were of the predominantly ventricular type or vice versa. And again, the patients with the ventricular type showing left premature contractions would at some time show right premature contractions and vice versa. This suggests that the causal factor of the premature contraction operates on both auricles and ventricles in the same heart even though it may show a marked preference for one or the other of the chambers.

PARASYSTOLE

In studying the relationship between the premature contractions and the normal beats, using the long strips of five minute electrocardiograms, no convincing evidence could be found in the strips examined that the premature contractions were responses to impulses belonging to a rhythmic series with a center of impulse formation independent of the sinus and functioning simultaneously with it. This is in accord with the findings of Iliescu and Sebastiano.[3] Strips were selected from our electrocardiograms, six with auricular and four with ventricular premature contractions. The following types were included:

1. Auricular premature contractions showing an apparently constant focus (in which the auricular aberrations signalling the inception of a premature contraction were all alike).

2. Auricular premature contractions which on superficial inspection appeared to be regularly recurrent.

3. Constant auricular bigeminy and trigeminy.

4. Ventricular premature contractions with constant focus.

5. Ventricular premature contractions appearing to be regularly recurrent.

6. Ventricular bigeminy and trigeminy.

These were timed in one one-hundredth seconds, measuring the R-R interval, beat by beat in each, and checking over the P-R intervals to eliminate variation in auriculoventricular conduction as a source of error. While the comparator was not used in these calculations, they were accurate to at least the one-fiftieth second and, furthermore, any errors resulting because of not using it in making the calculations would only tend to strengthen the evidence for the hypothesis of parasystole, rather than the

3. Iliescu and Sebastiano: Heart **10**:102.

reverse. In no strip examined could any simple mathematical time relationship between the premature contractions be said to hold with the same constancy as in the normally beating heart. In the strips showing bigeminy and trigeminy no simple time relationship was in evidence between the premature contraction and the normal beat preceding it. If any rhythmic independent focus governs the production of the premature contraction, it is profoundly influenced by the normal contractions whenever they cross its time for recurrence for it usually was following a supposed "silenced response" that the greatest variations occurred.

There was no evidence found to support the hypothesis of parasystole in the cases examined.

REST IN BED

Rest in bed alone had absolutely no effect on the premature contractions quantitatively or qualitatively; i. e., it did not lessen the number of the premature contractions per minute nor did it alter the focus, nor did it make a variable focus constant.

HEART RATE

Below rates of approximately 100 per minute, the heart rate bears no relation to the number of premature contractions occurring per minute. For example, a patient with a normal resting rate of 90 to 100 might have as many premature contractions per minute as another patient with a normal resting rate of 60. Furthermore, in any single patient there was no relation between the number of premature contractions per minute and the heart rate, provided the rate was below approximately 100 per minute. After passing the rate of about 100, the number of premature contractions per minute tended to diminish and this diminution was in direct proportion to the rise in rate.

Rest in bed had no effect on, and heart rate within the limits of 50 to 100 per minute had no relation to, the number of premature contractions prevailing.

EFFECT OF EXERCISE

Exercise practically always increased the number of premature beats. The usual effect was as follows: While the rate was high, for the short interval following the exercise, the number of premature contractions were diminished or absent; but as soon as the rate fell below approximately 100 per minute the number of premature contractions were always increased and continued so for a short while thereafter. It was common to see cases with auricular premature contractions develop some ventricular premature contractions following exercise and vice versa. The diminution in the number of premature contractions immediately following exercise seems to be due simply to the rise in rate, because in those patients in whom the exercise failed to increase

the rate to or above about 100 per minute, there was no diminution in the number of premature contractions.

One patient (case 8, table 1) responded as all others during his control period. When full doses of digitalis removed the premature contractions none appeared following exercise to breathlessness. Three patients (cases 9, 11 and 12) were too sick to try exercise. Patient 1 responded as all others during his control period. Later, when practically free of premature contractions while under quinine, an increase in the number of premature contractions appeared following exercise.

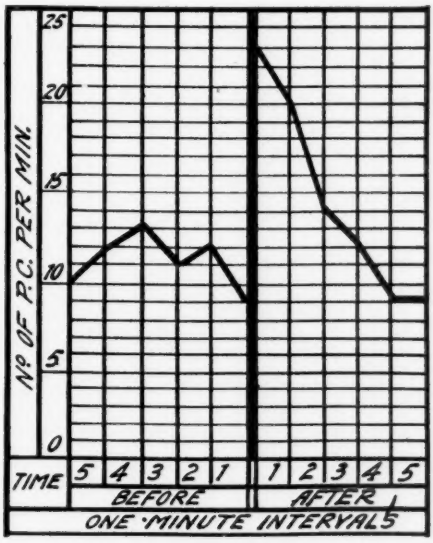

Chart 1.—Effect of exercise.

Chart 1 is a graphic representation of the effect of exercise on the number of premature contractions.

Table 2 is a random selection of the protocol figures of the study of the effect of exercise. In all there were thirty experiments done.

Following exercise, the number of premature contractions prevailing were increased.

EFFECT OF ATROPINE

Atropine was the first drug given following the control period. It was administered to all twelve patients. In six of them, a small dose, $\frac{1}{100}$ grain atropine sulphate was given first hypodermically. One hour later two doses each of $\frac{1}{30}$ grain were injected hypodermically twenty minutes apart. In the remaining six cases the preliminary small dose

TABLE 2.—*Effect of Exercise in Ten Experiments*

	1		2		3		4		5		6		7		8		9		10	
	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated
One Minute Readings Before Exercise	90	26	70	19	80	12	66	22	54	10	58	8	54	9	62	1	58	4	54	10
	80	24	68	20	82	11	66	20	54	11	58	12	54	7	62	3	56	3	54	12
	80	21	68	18	80	12	64	22	52	10	58	10	54	8	62	2	56	4	54	13
	80	26	70	21	82	13	64	20	52	12	58	9	54	8	62	0	56	4	54	11
	70	24	70	19	80	11	64	21	52	9	58	10	54	7	62	2	58	3	54	12
One Minute Readings After Exercise	100	34	120	34	120	4	126	14	90	3	85	15	90	15	110	4	104	6	100	8
	96	38	100	36	100	13	100	30	78	20	78	15	63	24	80	13	76	11	80	23
	94	32	100	36	90	18	80	38	70	16	72	16	60	20	68	11	66	21	66	20
	90	26	90	33	80	19	74	38	66	16	72	10	60	18	62	9	64	19	66	14
	80	19	80	30	65	17	64	30	60	18	58	6	60	12	62	4	60	16	54	12

The heavy horizontal line in the center indicates the period of exercise.

was omitted. Five minute electrocardiograms were taken every hour during the day of administration of the atropine.

The first small dose was given to produce the vagal stimulating effect and the second two doses to produce complete vagal paralysis. In this way, it was thought that a comparison between vagal stimulation and vagal paralysis might be brought out. Practically no evidence of vagal stimulation was obtained using the heart rate as the indicator.

Atropine had no effect on the number of premature contractions except in one patient (case 4, table 1) in whom the heart rate rose to 120 per minute and the premature contractions disappeared, the heart rate returning to 94 per minute in the next hour with the resumption of about the same number of premature contractions. This was in a patient with auricular premature contractions.

TABLE 3.—*Effect of Atropine in Six Experiments*

	1		2		3		4		5		6	
	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated
Five Minute Readings 1 Hr. Apart Before Atropine	62	8	86	23	60	9	90	26	74	0	70	12
	62	3	86	19	60	6	88	24	72	0	70	14
	68	12	86	22	60	10	90	32	72	0	72	13
	66	20	86	18	60	7	90	31	72	0	70	13
Dose, grains	1/100		1/100		1/100		1/100		1/100		1/100	
½ hour after	60	8	86	22	52	7	80	34	72	0	68	14
Dose, grains	1/15		1/15		1/15		1/15		1/15		1/15	
Five Minute Readings 1 Hr. Apart After Atropine	64	3	94	23	64	7	100	28	82	0	80	12
	60	6	100	21	68	12	120	0	104	0	100	15
	60	11	96	20	64	11	94	31	96	0	98	14
	60	8	100	18	60	13	90	30	96	0	96	15

In case 4 the absence of the premature contractions with the high heart rate and the absence of a definite effect following the drug in all should be noted.

All the patients given atropine developed other marked symptoms of atropinism, viz., dilated nonreacting pupils, dry, parched tongue and throat and some slight dizziness and mild delirium. Table 3 contains the protocol figures of the six atropine experiments with the preliminary small dose of the drug.

Atropine in full doses had no effect on the number of premature contractions prevailing, except when it produced a marked rise in the heart rate.

EFFECT OF EPINEPHRINE

A solution of epinephrine chloride, 1:1,000, was administered hypodermically in doses of 15 minims in eighteen experiments. Electro-

cardiograms of one minute duration were taken every five minutes during the study, usually five electrocardiograms before and five after the injection.

The results were uniform. There was considerable increase in the number of premature contractions occurring per minute, beginning five minutes after the injection and lasting for thirty minutes to one hour. There was only a slight rise in the heart rate.

Patients with auricular premature contractions frequently developed ventricular premature contractions and vice versa. Patients with right ventricular premature contractions often developed left ventricular pre-

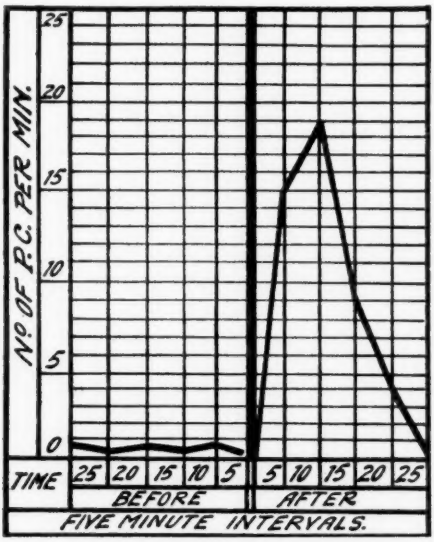

Chart 2.—Good reaction following injection hypodermically of 15 minims of epinephrine.

mature contractions and vice versa. Two premature contractions occurring together were not infrequent in the patients with ventricular premature contractions. In one patient with the ventricular type three premature contractions in series appeared frequently with the focus variable. In one patient with the auricular type, groups of four and five premature contractions in succession occurred.

Regular patterns of appearance of the premature contractions were frequent, where they were not in evidence before the injection. Thus trigeminy was common and short periods of bigeminy appeared in one patient with ventricular premature contractions (case 5, table 1). No

variation from the basic normal rhythm predominating ever occurred following the injection.

One patient (case 1, table 1) with predominantly auricular premature contractions, while practically free of premature contractions under quinidine therapy, developed considerable numbers of them following the epinephrine and lasting for one hour and fifteen minutes.

Another patient (case 8, table 1) with premature contractions of predominantly ventricular type reacted as all others with a marked increase following the epinephrine, but when free of premature con-

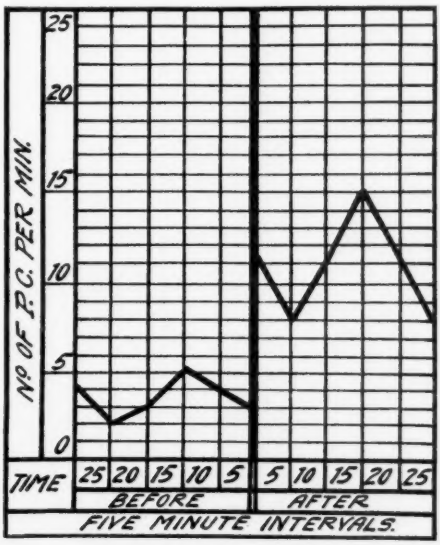

Chart 3.—Poorest result in eighteen experiments of hypodermic injection of 15 minims of epinephrine.

tractions during six weeks of digitalis therapy developed no premature contractions following another injection of epinephrine. Four weeks after the digitalis was discontinued no premature contractions had reappeared. Epinephrine injected at this time still failed to call forth premature contractions.

Table 4 contains the protocol figures of nine of the epinephrine experiments, and charts 2 and 3 contain the results of a slight reaction to epinephrine and a marked one, represented graphically.

Epinephrine increased the number of premature contractions prevailing.

TABLE 4.—*Effect of Epinephrine in Nine Experiments*

	1		2		3		4		5		6		7		8		9	
	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated	Heart Rate	Premature Contractions per Min., Calculated
Before	76	14	94	3	70	0.5	62	6	100	36	100	22	76	10	96	19	56	0.4
	78	15	94	2	70	0.4	66	7	100	40	96	21	76	5	90	17	58	0.2
	78	14	94	3	70	0.5	64	7	100	37	96	22	76	6	90	18	58	0.5
	78	16	96	3	70	0.5	64	7	100	35	96	22	76	5	90	20	56	0.2
	75	16	92	3	66	0.5	64	7	100	36	96	19	76	6	90	19	58	0.4
After	80	20	94	8	86	13	66	9	100	38	90	26	76	13	90	26	58	0
	100	23	100	12	84	13	68	15	100	55	90	28	76	10	90	23	60	15
	100	27	98	14	80	9	68	17	100	63	90	30	92	24	90	26	64	19
	100	27	98	12	80	4	70	17	100	62	90	27	88	18	90	30	66	8
	100	20	98	7	76	0.3	66	17	100	65	90	24	76	16	90	23	58	4
	...	..	..	..	..	..	..	..	100	54	..	..	..	..	..	..	56	2
	...	..	..	..	..	..	..	..	...	..	..	..	..	..	..	..	58	0.6

In each experiment five one minute electrocardiograms were taken five minutes apart before injection; the heavy horizontal line in the center indicates injection of epinephrine, 15 minims, hypodermically; following this five one minute electrocardiograms were taken five minutes apart.

QUININE BY INTRAVENOUS INJECTION

Quinine dehydrochloride in solution of 1:30 was injected intravenously during a period of five to eight minutes into each of eight patients, four with auricular and four with ventricular contractions. Control electrocardiograms of five minutes' duration were taken at approximately two hours, one hour, one-half hour, and immediately before injection. In the first three cases, tracings were taken during the injection. In all cases, tracings were taken immediately after injection, and after approximately fifteen minutes, one-half hour, one hour,

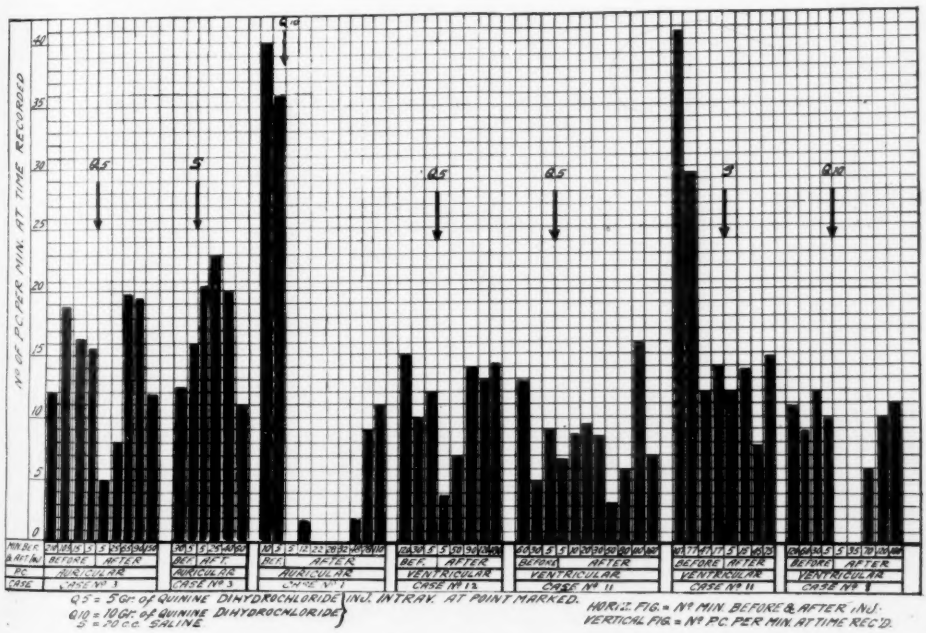

Chart 4.—Effect of injection of quinine.

two hours and three hours. In two instances physiologic sodium chloride solution was injected for purposes of control. It was without effect on the premature contractions and was therefore not repeated in the subsequent experiments. In the auricular group, two patients received 5 grains (0.32 Gm.) of quinine and two received 10 grains (0.65 Gm.). Of those given 5 grains, both showed marked diminution of the number of premature contractions per minute immediately following the injection. The effect had entirely disappeared within one hour.

Of those given 10 grains, one showed marked diminution in the numbers of premature contractions occurring (about 50 per cent), last-

ing for two and one-half hours after the injection. The other (case 1, table 1) showed complete absence of the premature contractions for thirty-two minutes following the injection, followed by a gradual increase. After one hour and forty minutes they had barely returned to half their original number. Before injection this patient had a practically continuous bigeminal rhythm with a rate of 66. During the thirty-two minutes regular rhythm following the injection, the heart rate was 50 per minute. For the first ten to fifteen minutes the electrocardiograms of this patient showed an absence of the P wave. Then it gradually reappeared.

Of those with ventricular premature contractions, two patients received 5 grains and two received 10 grains. Of those receiving

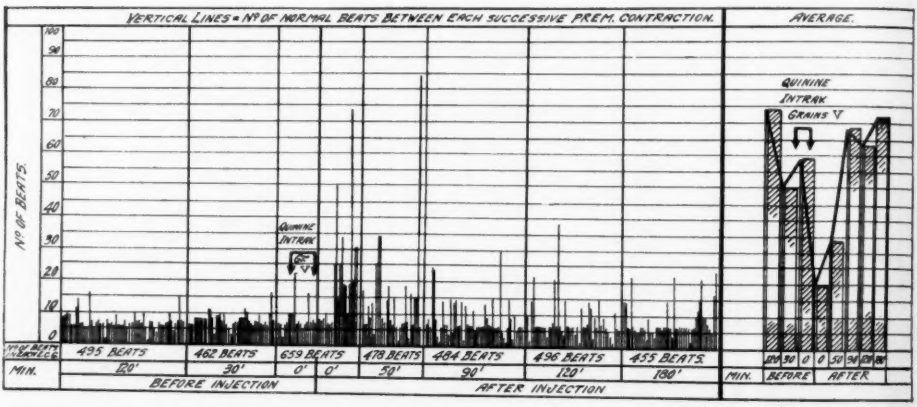

Chart 5.—Effect on premature contractions of quinine injected intravenously.

5 grains, one showed diminution of the number of premature contractions to approximately one third of the original number, immediately after the injection and returning to the original level in about ninety minutes. In the other case there was no effect. Of those given 10 grains, in one there was complete disappearance of the premature contraction for one hour with gradual return to the original number. In the other patient there was almost complete disappearance for thirty minutes with return to the original number at the end of two hours. In all instances there was a reduction in the ventricular rate not exceeding ten beats per minute with the exception of one patient, already mentioned.

In no instance, with the exception of the one case in which it is described was there any change in the P waves, P-R intervals, Q-R-S complexes, T waves or preponderances.

There was no selective action observable in the effect of quinine on the various types of premature contractions, auricular, right ventricular or left ventricular.

The manner in which the premature contractions were diminished was curious and worthy of mention. It was common to all. Chart 5 illustrates the point. Whereas before the injection, the pattern of the premature contractions was fairly constant, running for example 2/7/1/1/7/1/6/1/7/2/6/3/, etc., after the injection, the diminution of the total number of the premature contractions occurred principally by long periods of normal beats inserted into the original pattern, for

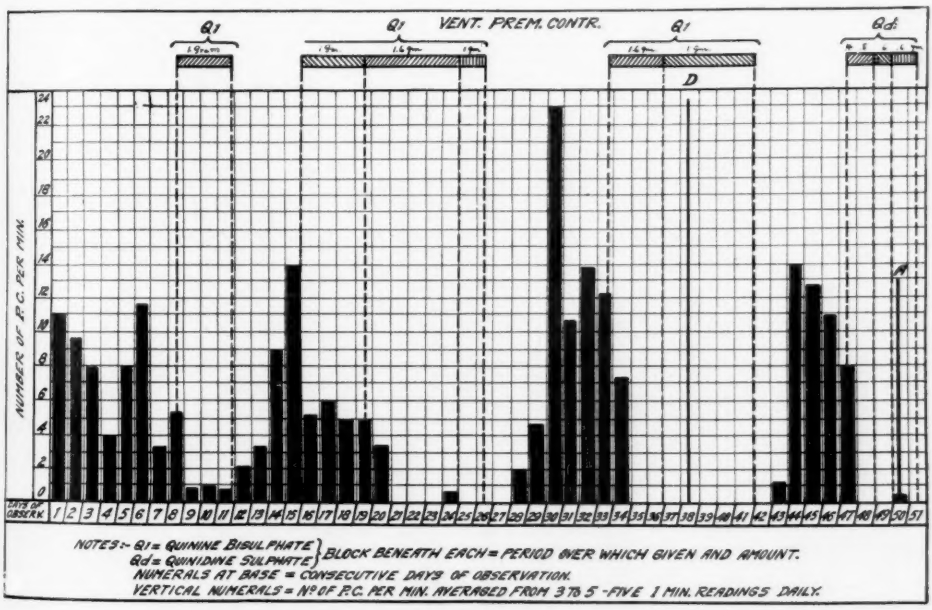
Q1
Q1
VENT. PREM. CONTR.
Q1
Qd
D
NUMBER OF P.C. PER MIN.
DAYS OF OBSERV.
NOTES:- Q1 = QUININE BISULPHATE
Qd = QUINIDINE SULPHATE
BLOCK BENEATH EACH = PERIOD OVER WHICH GIVEN AND AMOUNT.
NUMERALS AT BASE = CONSECUTIVE DAYS OF OBSERVATION.
VERTICAL NUMERALS = Nº OF P.C. PER MIN. AVERAGED FROM 3 TO 5 - FIVE 1 MIN. READINGS DAILY.

Chart 6.—Effect of quinine in case 11.

example, 7/1/6/1/50/80/7/6/70/6/1/, etc. It never occurred by a uniform change in the pattern, for example, 15/15/14/12/18/17/15/, etc. Chart 4 illustrates the reaction to quinine by intravenous injection.

In eight patients in whom quinine was injected intravenously, premature contractions were abolished in two, diminished in five and unaffected in one.

QUININE BY MOUTH

Following the intravenous injection of quinine dihydrochloride, the bisulphate was always administered by mouth in doses of 0.3 Gm. starting with two doses daily and increasing to three, then four, a total of

1.2 Gm. a day. In every case the dose was increased until premature contractions disappeared or symptoms of cinchonism supervened. It was administered to twelve patients, four with auricular premature contractions and eight with ventricular premature contractions.

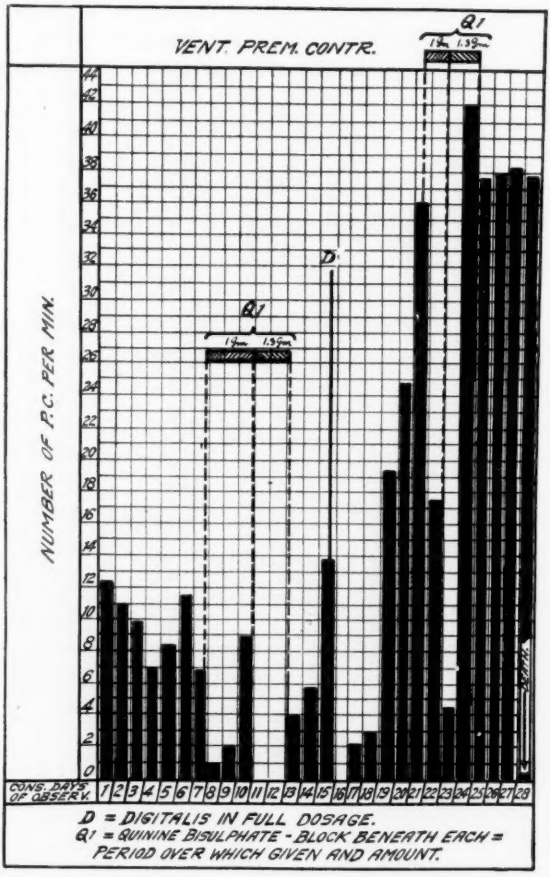
VENT. PREM. CONTR.
Q1
1.2 gm. 1.2 gm.
D
Q1
1.2 gm. 1.2 gm.
NUMBER OF P.C. PER MIN.
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
CONS. DAYS OF OBSERV.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
D = DIGITALIS IN FULL DOSAGE.
Q1 = QUININE BISULPHATE - BLOCK BENEATH EACH = PERIOD OVER WHICH GIVEN AND AMOUNT.

Chart 7.—Effect of quinine by mouth in case 12.

Among the four with auricular premature contractions, three had considerable diminution of the total number of premature contractions per day. In one of these (case 3, table 1), a very great diminution occurred the first day, followed by a gradual increase in their number, in the succeeding days without ever reaching the original level. The same was true of the other two to a lesser extent. In the fourth

patient (case 1, table 1) complete abolition of the premature contractions occurred and was maintained by 0.3 Gm. three times daily. This continued for two weeks, after which time the premature contractions began to appear in varying numbers. The dose was raised to 0.3 Gm. every four hours, which again abolished them, but tinnitus supervened after three days on this dosage and the drug had to be discontinued. Subsequent administration of 0.3 Gm. three times daily produced a marked diminution but there was a distinct tendency toward a gradual increase in the number of premature contractions despite the continued administration of the drug ("escape").

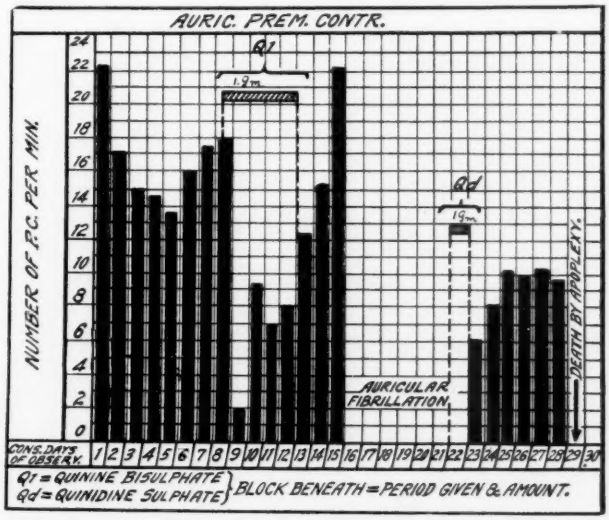

Chart 8.—Effect of quinine and quinidine by mouth in case 3.

Among the eight patients with ventricular premature contractions, in only one case (case 11, table 1), of arteriosclerosis with a hopeless prognosis, did quinine abolish the premature contractions entirely. In this patient administration and withdrawal was tried three times and in all the results were the same, although at different times the same dose was not equally effective.

All other cases showed diminution in the number of premature contractions to varying degrees, with the characteristic tendency to "escape" being always present. Increasing the dosage, which was done in all until symptoms of cinchonism appeared, repeated the foregoing phenomenon. In those patients with failure no improvement of the circulation occurred.

The two patients showing complete disappearance of the premature contractions under this therapy stated that they felt better, because the annoying "jumping of the heart" had disappeared.

Charts 6, 7 and 8 illustrate samples of reaction while under quinine therapy.

Quinine administered by mouth reduced or abolished the premature contractions in the patients observed.

QUINIDINE BY MOUTH

Quinidine was given in doses beginning with 0.2 Gm. twice daily and increasing to once every four hours as the case demanded. The results with quinidine differed from those with quinine only in the fact that

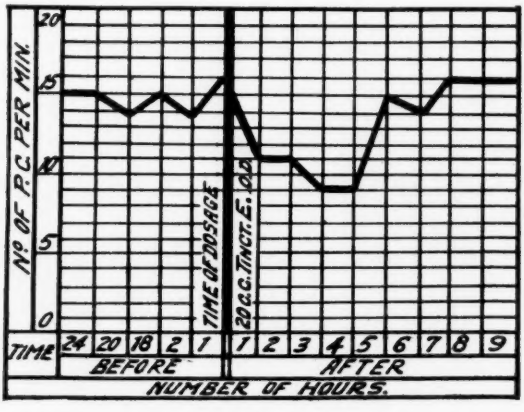

Chart 9.—Effect of digitalis in full dosage in case 7; case 9 gave practically the same results.

quinidine was more potent in reducing the number of premature contractions. In cases in which quinine entirely abolished them, quinidine did likewise; in cases in which quinine diminished them quinidine did so to a greater degree than the quinine. Likewise the characteristic "escape" of the premature contractions from the influence of the drug was less in degree.

Quinidine administered by mouth reduced or abolished the premature contractions.

EFFECT OF DIGITALIS

The eight patients studied were given from 0.1 to 0.15 of a cat unit of the tincture of digitalis per pound of body weight in one or two doses, and three cat units per day thereafter. During the day of the full digitalization electrocardiograms of five minutes' duration were taken hourly.

There were two patients with predominantly auricular and six with predominantly ventricular premature contractions.

Of the two patients with auricular premature contractions, one (patient 1, table 1) showed practically complete disappearance of the premature contractions following the administration of the digitalis, and continued so during the entire time of exhibition of the drug. Withdrawal resulted in the gradual return of the premature contractions to the original number. Readministration in the same way yielded the same result. In this patient, digitalis was unintentionally administered to minor toxic symptoms (nausea and vomiting). No increase in the

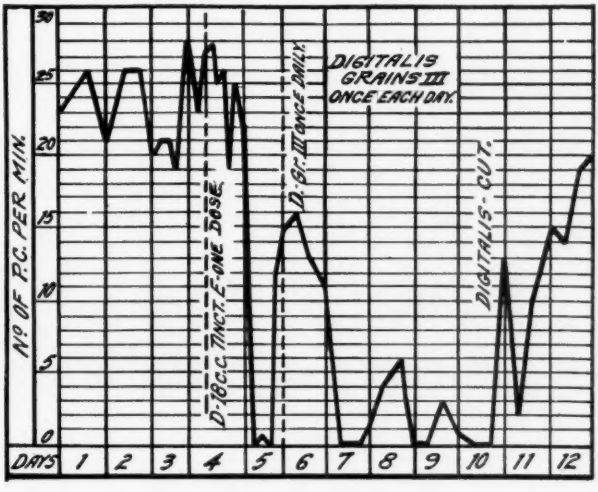

Chart 10.—Effect of digitalis in full dosage in case 4.

number of premature contractions occurred. In the other patient (case 4, table 1), digitalis so given caused a marked diminution in the number of premature contractions.

Among the six patients with ventricular premature contractions, two (cases 5 and 8, table 1) showed complete disappearance of the premature contractions following the administration of the drug. In one of these (case 8, table 1), made the subject of a separate report, this was studied in detail and repeated twice.

In two other patients, both terminal (cases 11 and 12, table 1), a very marked increase in the number of premature contractions appeared about twelve hours after administration of the drug, this occurring at one observation only (in charts 6 and 7, marked *D;* in chart 6 also comparative epinephrine reaction, marked *A*, should be noted). The

observation has not been repeated since and the question as to whether it resulted from the digitalis or was coincidental cannot be decided. In one of these (case 11), this occurred while free of premature contractions under quinine (this patient is not included in the digitalis series because of the simultaneous quinine administration). The other patient showed marked but temporary diminution following the increase. This lasted for two days and was again followed by a marked increase in the number of premature contractions until death six days later.

One patient (case 10, table 1) showed considerable diminution. In the remaining two patients digitalis had no noticeable effect (chart 9). Charts 9, 10 and 11 illustrate the types of reaction to digitalis.

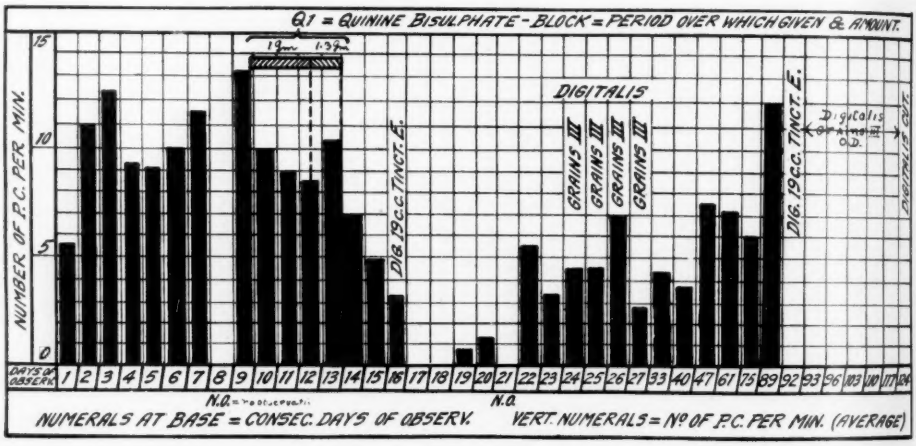
Q.1 = QUININE BISULPHATE - BLOCK = PERIOD OVER WHICH GIVEN & AMOUNT.
NUMBER OF P.C. PER MIN.
DIGITALIS
GRAINS III
GRAINS III
GRAINS III
GRAINS III
DIG. 19 c.c. TINCT. E.
DIG. 19 c.c. TINCT. E.
Digitalis
DAYS OF OBSERV.
N.Q.
N.Q.
NUMERALS AT BASE = CONSEC. DAYS OF OBSERV.
VERT. NUMERALS = Nº OF P.C. PER MIN. (AVERAGE)

Chart 11.—Effect of digitalis in full dosage in case 8.

Digitalis in large doses caused diminution to complete disappearance of the number of premature contractions present in six of eight patients studied.

SUMMARY AND COMMENT

In general, rest in bed and atropine had no effect on the number of premature contractions. Exercise and epinephrine increased the number. Quinine, quinidine and digitalis decreased the number. These results appeared to be qualitatively, but not quantitatively, constant and unrelated to the type of the premature contraction or the etiologic, anatomic or functional type of heart disease in which they occurred. This represents only a small group of patients. Whether a relationship between these factors does exist remains for further study to establish.

References are commonly made in the literature to the beneficial effects of the withdrawal of coffee, tea, tobacco, alcohol, etc., in patients

with premature contractions. Undoubtedly such measures do diminish or abolish the premature contractions in certain cases. There is, however, a large group of patients in whom such measures are without effect. In the latter group, there is recourse to quinine, quinidine or digitalis. Quinine appears to be the least satisfactory because of the large dosage necessary and the early supervention of cinchonism. With quinidine the results are better but the tendency of the premature contractions to "escape" demands increasingly larger doses. The results of our studies indicate that both of these drugs have a limited field of usefulness in the treatment of patients with premature contractions and, furthermore, that digitalis deserves a more prominent place in the treatment of the premature contraction than it has heretofore received. A careful study of our records indicates in nearly all cases there was a considerable reduction in the number of premature contractions or their total abolition at some time during its administration. To obtain more satisfactory results with digitalis appears to be largely a question of proper dosage. A study along these lines is at present in progress.

THE RATIONALE OF THERAPEUTIC PUNCTURE IN PERICARDIAL EFFUSIONS

AN EXPERIMENTAL STUDY *

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Are patients with pericardial effusions aspirated early and often enough? Are patients with simple serous effusions permitted to die as the result of increasing intrapericardial pressure because of the lack of aspiration? If these two questions are answered in the affirmative why do we fail so often to institute this remedial measure?

We raise these questions because in the last few years one of us (C. S. W.) has had under his direct observation four cases of pericarditis with effusion of a simple serous character in which, according to his best judgment, life might have been saved if aspiration had been employed. To justify this statement a brief synopsis of these cases is here given.

REPORT OF CASES

CASE 1.—I was called late in the forenoon by my intern at the hospital who stated that a patient had been admitted the night before with what he believed to be a pericardial effusion. A to-and-fro rub was audible all over the front of the heart, but I was told over the telephone that the signs of effusion were definite. Knowing my interest in this disease he asked me if I would come over to see the patient. The patient's pulse, I was told, was fairly good and he thought there was no impending danger. I arranged to see the patient that afternoon. At perhaps 1 p. m. I was again called to the telephone and told that the patient's pulse had grown very much weaker within the previous half-hour. I left for the hospital immediately, found the situation to be exactly as represented and was preparing to do a puncture when the patient suddenly died. This is the patient referred to in a previous article as experiment 27.[1] We aspirated all the fluid we could obtain a few minutes after death and immediately injected the same amount, namely 270 cc., of agar solution. After this had thoroughly hardened, the pericardial sac with the great vessels were removed and a cast made of them. It may be noted that the total amount of the exudate, as determined by the measurement of the cast by the displacement method, was 405 cc. This case is a peculiarly instructive one in that the pressure conditions were precisely the same as during life. From an inspection of the cast of the heart the great veins and auricles especially were seen to be flattened out and this must have been their condition in the last moments of life. As was said in the previous study, one cannot help but believe that death in this case was actually the result of extensive pressure and that had the fluid been aspirated the pressure factor at least would have been removed.

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* From the department of medicine of the University of Illinois College of Medicine.

1. Williamson, C. S.: Pericarditis with Effusion, Arch. Int. Med. **25**:222 (Feb.) 1920.

CASE 2.—A patient with a small right lower lobar pneumonia was seen in consultation. The patient did very well, so well in fact that a second consultation, which had been arranged for a few days later, was deemed by the attending physician to be unnecessary. Some days later I was summoned in great haste to take the first train to see the patient again. As he lived in an adjoining state, I was three or four hours in reaching him. On my arrival I obtained the following history: The temperature had been normal, or approximately so, for some days, but the patient had been developing considerable dyspnea. The family physician had considered that he was dealing with a greatly dilated heart. The pulse had been good until about an hour before I had been sent for, when it had suddenly become much weaker and this was the immediate reason for my having been summoned. A roentgenogram of the heart had been taken a few hours before and a few moments' study of it was sufficient to make an almost positive diagnosis of a moderately large pericardial exudate. Proceeding to the patient's room I found him in extremis and death ensued while a needle was being sterilized to puncture the pericardium. As there was some skepticism as to the correctness of the diagnosis, we proceeded as if the patient were still living and punctured the sac, with the result that a slightly turbid fluid under very high pressure spurted out of our needle. A necropsy was not permitted, but the velocity of flow was so great as to leave no doubt as to the degree of pressure in the sac.

CASE 3.—This patient had a simple serous pericardial exudate following a severe tonsillitis and rheumatic fever. The fluid accumulated with considerable rapidity and it became evident that the intrapericardial pressure was rapidly increasing, since the dyspnea was growing greater and the blood pressure steadily going down. Permission to aspirate the pericardial sac was refused and a consultation with a colleague was insisted on and arranged. A few hours later the exitus lethalis occurred rather suddenly. Permission to examine the heart was obtained and disclosed about 500 cc. of a serofibrinous exudate. Aside from a beginning verrucose endocarditis of minimal extent there were no significant postmortem findings.

CASE 4.—This patient was a boy, aged 18, who went to the hospital with a temperature of 101 and with some substernal pain. He had just recovered a week or two before from a severe case of polyarthritis and tonsillitis. The remainder of the history was unimportant. Physical examination on the first day left us in doubt as to the actual existence of an effusion, but this doubt was quickly dispelled the next day when it became plain that not only was fluid present but present also in considerable quantity. A roentgenogram taken about thirty-six hours after admission was characteristic. The patient's general condition was fairly satisfactory. On admission the pulse rate was 120 and the blood pressure about the same. The patient was shown in clinic to have a typical pericardial effusion and a second roentgenogram showed a much larger exudate than before. It was then decided to aspirate as the blood pressure was beginning to fall and the patient had grown very dyspneic. My interns, who carried out the aspiration, removed only 250 cc. and another roentgenogram taken a few hours after the aspiration showed little change in the outline of the effusion. The patient apparently improved markedly, but some days later died suddenly and unexpectedly. As a necropsy could not be obtained it cannot be stated with certainty just what the conditions were. It is, however, a fair question whether if more fluid had been removed the first time, or if a second puncture had been made, the pressure might not have been sufficiently relieved to make recovery possible.

In our opinion the characteristic thing about the deaths of these patients is that they occurred suddenly. All were supposed to be in fairly good condition, as judged by the usual clinical criteria, and yet shortly after they died. This type of death may be conveniently referred to as the pericardial death and occurs only or principally in such cases as are substantially uncomplicated.

A study of a number of accessible records, principally from the Cook County Hospital, disclosed briefly the following facts: Among fifty-four fatal cases of pericarditis with effusion there were nine in which no puncture was carried out and in which it seemed reasonable to believe

TABLE 1.—*Experiment E*

Dog 11; weight, 12 Kg. Nov. 24, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
10:30:	0	—5	60
10:30:24	10	—5	60
10:30:54	14	—3	54
10:32:12	40	+1	50
10:33:18	48	11	30
10:34:06	58	23	18
10:34:48	66	29	6
10:35:24	76	37	—2
10:36:36	0	Clot	50

TABLE 2.—*Experiment D*

Dog 11; weight, 12 Kg. Nov. 24, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
9:05	0	—5	55
9:06	4	0	55
9:07	6	29	60
9:08	14	33	60
9:08:36	22	39	50
9:09:24	26	43	45
9:10:06	30	49	35
9:10:54	34	59	25
9:11:42	44	69	15
9:12:30	50	79	0

Some of the tracings did not reproduce well, but they can readily be reconstructed from the data in the tables.

TABLE 3.—*Experiment F*

Dog 11; weight, 12 Kg. Nov. 24, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
10:15	0	—2	50
10:16	16	—13	50
10:17	34	—13	50
10:19:42	46	33	40
10:20:54	58	53	26
10:21:30	70	63	16
10:22:24	84	81	10
10:23:18	94	87	0
10:24:18	108	101	—8
10:25:42	0	47	100
10:27:12	0	30	80

that by this procedure life might surely have been prolonged and possibly or even probably rescued. In four other cases it would have probably been of great benefit, if not life saving. If these conclusions are even approximately correct it seems clear that we clinicians have

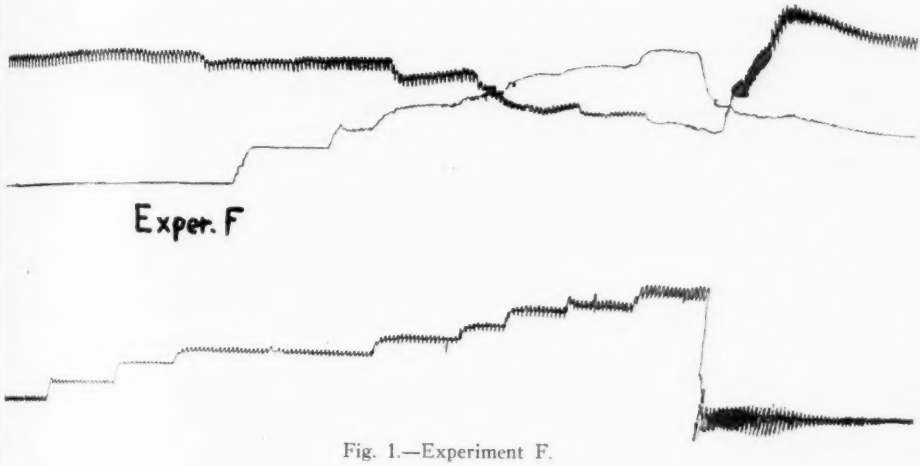

Fig. 1.—Experiment F.

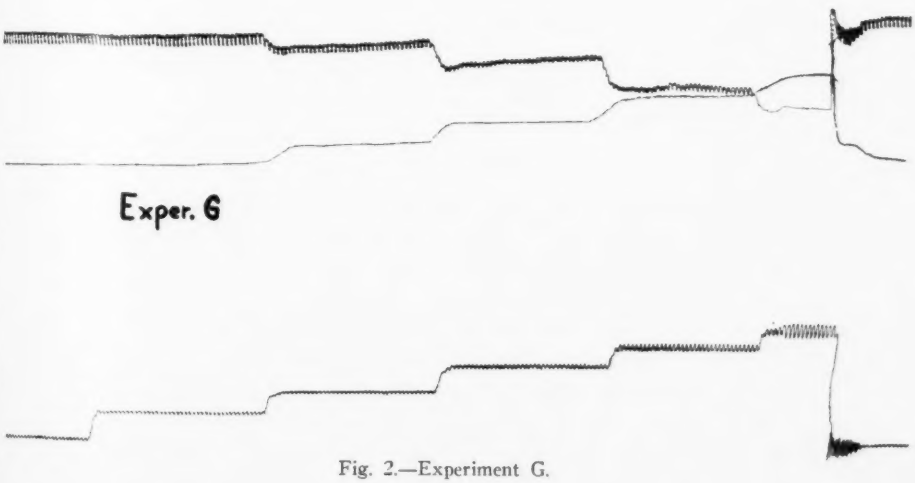

Fig. 2.—Experiment G.

been permitting patients with pericardial effusion that has been correctly diagnosed to die for the lack of a timely carrying out of a simple therapeutic procedure.

Practically all writers on this subject from François Franck to the present time are unanimous in the opinion that the circulation comes to

TABLE 4.—*Experiment G*

Dog 12; weight, 10 Kg. Nov. 25, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
11:15	0	—8	75
11:17:30	22	—6	75
11:19:48	40	12	65
11:22:12	60	32	45
11:24:12	76	52	15
11:25:12	82	70	5
11:26:24	0	—8	80

TABLE 5.—*Experiment H*

Dog 12; weight, 10 Kg. Nov. 25, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
11:10	0	5	55
11:11:24	20	3	55
11:14:06	40	13	50
11:15:18	62	33	45
11:16:12	78	51	20
11:17:48	88	62	8
11:18:54	98	78	—4
11:19:48	110	88	—8
11:21	0	—5	+75
11:21:48	0	—5	60

TABLE 6.—*Experiment I*

Dog 12; weight, 10 Kg. Nov. 25, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
9:25	0	—2	45
9:27:06	20	10	45
9:28:36	42	24	35
9:30:06	66	44	7
9:31:54	78	58	—7
9:33:24	88	66	—15
9:34:24	100	74	—20

The pericardial cannula was 10 cm. above the table and the leveling bulb 30 cm. above when the heart stopped.

an end at the instant when the intrapericardial pressure equals that in the cavae. Indeed, this would seem almost self-evident. While this is, comparatively speaking, simple enough to understand in the experimental animal, we have no clinical means at our disposal to measure the intrapericardial pressure and have therefore no means of knowing when this begins to approximate the pressure obtaining in the cavae, since this

is in reality the real guide for therapeutic puncture. In the cases cited a correct interpretation of what was going on in the pericardial sac might have saved the patients' lives. Our study was undertaken to determine the relations between arterial, venous and intrapericardial pressures in animals with artificial pericardial effusions, hoping thereby to gain additional points of prognostic and therapeutic value.

CONDITIONS OF EXPERIMENT

Dogs were used and under light ether anesthesia tracheotomy was performed and a cannula inserted into the right carotid artery and another into the left external jugular vein in such a manner that the

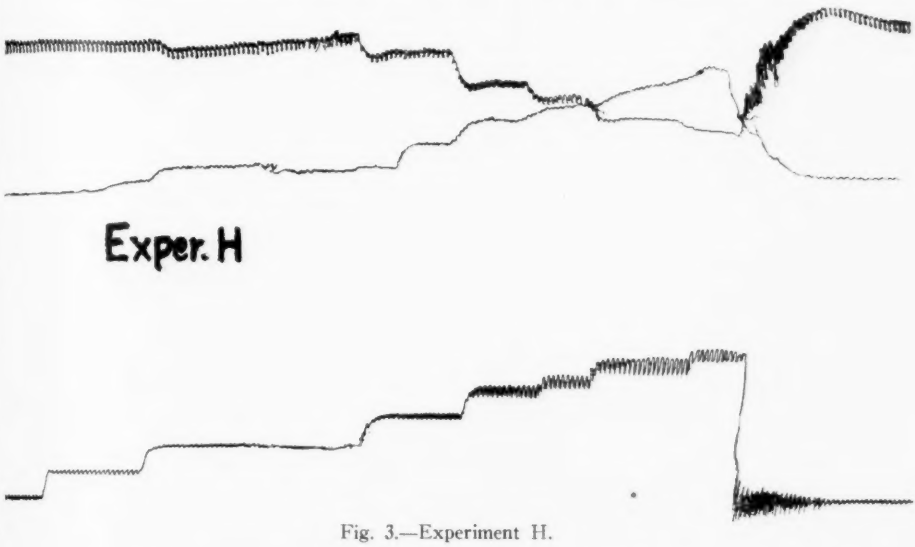

Fig. 3.—Experiment H.

arterial and venous pressure changes could be recorded by means of manometers writing on a smoked drum. A vertical incision was next made between the ribs on the left side and the heart exposed, artificial respiration being instituted as soon as the thoracic cavity was opened. A T tube cannula was then tied into the pericardium and connected with a manometer writing on the smoked drum and also with a leveling bulb. Warm physiologic sodium chloride solution was used to produce pressure in the pericardium and this pressure could be regulated by means of the leveling bulb. Water was used in both the pericardial and venous and mercury in the arterial manometer. It should be noted that the venous cannula was tied in the vein centrally, so that the venous pressures recorded are not exactly comparable to those which might be taken clinically.

Each experiment was begun by recording the arterial and venous pressure before raising the intrapericardial pressure. The latter was then gradually raised by elevating the leveling bulb until it became so great that the heart stopped. At this point the bulb was quickly depressed so that the intrapericardial pressure was reduced to zero and

TABLE 7.—*Experiment J*

Dog 13; weight, 15 Kg. Nov. 27, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
9:40	0	11	50
9:41:19	4	11	50
9:42:38	6	11	50
9:44:38	14	13	50
9:48:14	22	13	50
9:50:56	26	21	45
9:54:32	34	28	35
9:57:32	40	40	—15
10:00:02	0	15	+35

TABLE 8.—*Experiment K*

Dog 13; weight, 15 Kg. Nov. 27, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
10:46	0	—6	75
10:47:24	10	—6	75
10:49:30	20	—6	75
10:51:36	25	+10	75
10:54:24	30	16	70
10:56:24	35	24	65
10:58:24	45	36	45
10:01:48	50	52	—15
10:03:24	0	4	+65

TABLE 9.—*Experiment L*

Dog 13; weight, 15 Kg. Nov. 27, 1925.

Time	Pericardial Pressure, Mm. Water	Venous Pressure, Mm. Water	Arterial Pressure, Mm. Mercury
10:07	0	—5	75
10:08	8	15	75
10:09	12	15	75
10:10:36	18	17	70
10:12:48	26	23	64
10:15:24	34	31	64
10:18:36	44	41	54
10:20:30	52	51	44
10:22:06	58	57	14
10:25	60	71	—20
10:27	0	23	+50

in each case the heart again quickly resumed its action. In each experiment the increase in pericardial pressure caused a steady rise in the venous and a steady fall in the arterial pressure. A time mark at six second intervals on the tracing enabled the recording of the time relations during the experiment. It is to be further noted that in a few of

Fig. 4.—Experiment J.

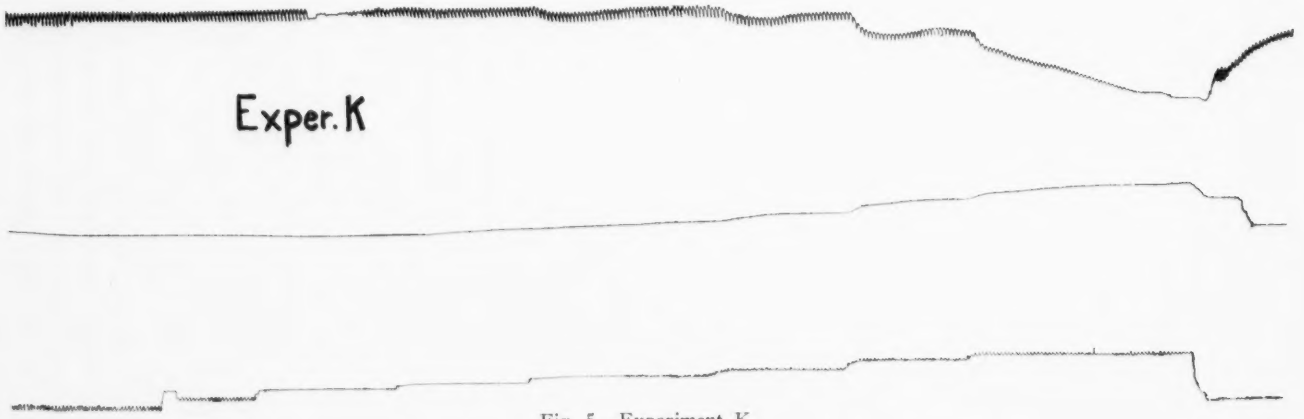

Fig. 5.—Experiment K.

these experiments the incision over the heart was closed and the dog respired naturally, i. e., without artificial respiration. As no difference was noted in these experiments artificial respiration usually was employed.

RESULTS

An inspection of the tables and the tracings shows that under our conditions of experiment a rather gradual raising of the intrapericardial pressure has for its invariable result the raising of the venous and the lowering of the arterial pressure. It will be further seen that for a given increment in the pericardial pressure these changes are more pronounced as this pressure becomes higher, so that as it approximates that which obtains in the vena cava, i. e., as it nears the point at which the circulation stops, the rise in the venous and the drop in the arterial pressure is more noticeable. That these phenomena are due to the increase in pericardial pressure alone is evident from the fact that even a partial release of it causes the venous pressure to drop and the arterial to rise immediately. In these respects our results are entirely in accord with those of other authors. If now we turn our attention to the more quantitative pressure relations it is obvious that the first slight increase in pressure produces insignificant changes on either the venous or arterial side. Further increase in the pressure in the pericardium produces a fairly steady drop on the arterial and a corresponding rise on the venous side and the latter changes are accentuated as the critical point; i. e., the point at which the circulation would stop is approached. We have already noted that our venous pressures, while not strictly comparable with the venous pressures as they might be taken clinically in an arm vein, would be roughly proportional to the latter.

If now we translate our findings into clinical practice it would seem that the following statements are justified: Measurements of the arterial pressure as carried out at the bedside enable one in a general way in cases of pericarditis, substantially uncomplicated, to prognosticate an increasing pressure in the pericardium. A steady fall in the arterial pressure, and especially a sudden increase in the rate of fall, indicates a near approach of the critical point, and calls for a therapeutic puncture. A steady rise in the venous pressure would enable the observer to predict the same event, but this is rarely done clinically, and its measurement is subject to a considerably greater error than the measure of the arterial pressure.

To make our points more clear, we append a number of tracings. In most instances, more than one tracing was taken from the same animal, showing that the increase of pressure to a point sufficient to stop the heart is quite compatible with, at least temporary, recovery. The tables have been constructed from data read off from the tracings. While

Fig. 6.—Experiment L.

thirteen dogs were used in all, and, as stated, in most cases several tracings taken one after another from the same animal, they were practically identical, so that, to economize space, only a few examples are given. The lowest line on the tracings indicates the intrapericardial, the middle line, the venous, and the top line the arterial pressure.

CONCLUSIONS

1. A not inconsiderable number of patients with substantially uncomplicated pericarditis with effusion die a typical pericardial death, that is, die as the result of the pressure of the exudate shutting off mechanically the great veins.

2. The pressure in the pericardial sac is the real criterion of the danger, and this is not proportional to the size of the exudate, but rather to the rapidity with which the effusion develops.

3. A steady fall in the arterial pressure and particularly a sudden increase in the rate of fall, is a direct indication for therapeutic puncture and relief of the pressure.

THE RELATION OF MONILIA TO INFECTIONS OF THE UPPER AIR PASSAGES*

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MOYER S. FLEISHER, M.D.
ST. LOUIS

The occurrence of yeasts or yeastlike organisms in the respiratory tract of normal or sick persons is by no means an unrecognized occurrence. It has long been accepted that fungi (named usually as monilia or endomyces) are agents in the causation of thrush. In recent years reports have appeared in increasing numbers concerning the presence of fungi in affections of the upper air passages of man. It has been shown by a number of observers that fungi can be found in the upper air passages of normal persons, and also, possibly as secondary invaders, in the air passages of persons suffering from infections apparently primarily due to some bacterial agent.[1] The presence of fungi, generally of the class of the imperfect fungi, has been demonstrated in a number of cases of bronchitis; such cases have been reported from various parts of the world but principally from the tropics.[2] And, finally, fungi of similar types have been demonstrated in pulmonary lesions[3] in which no other specific causative agent was shown to be present.

We are presented then with the facts that fungi imperfecti are to be found in the upper air passages of normal persons and also of persons with the lesions of either the mouth, the bronchi or the lungs. These organisms are to be found in certain conditions of disease and it often appears that their presence serves as the only recognizable factor to explain the causation of the particular disorder. It is difficult, therefore, to determine definitely the relationship of these fungi to disease.

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* From the Department of Bacteriology and Hygiene, St. Louis University School of Medicine.

1. Tanner and Dack: Centralbl. f. Bakteriol. **91**:282, 1924. Castellani: Ann. de l'Inst. Pasteur **30**:149, 1916.

2. Castellani and Chalmers: Manual of Tropical Medicine, Philadelphia, William Wood & Company, 1922, pp. 1886-1891. Steinfield, E.: J. Lab. & Clin. Med. **8**:744 (Aug.) 1923; Bronchomycosis Associated with Certain Types of Bronchial Asthma, J. A. M. A. **82**:83 (Jan. 12) 1924. Sur, T.: Indian M. Gaz. **56**:445 (Dec.) 1921. Castellani, A.; Douglas, M., and Thompson, E. T.: J. Trop. Med. **28**:257 (July 15) 1925.

3. Sanfilippo, cited in Rev. de med. **42**:104, 1925. Bullet: Medical Paris, 1921, p. 35. Jaumain, D., and Colard, A.: Compt. rend. Soc. de biol. **93**:858 (Sept. 30) 1925.

We have had the opportunity to study cultures from a number of patients suffering with infections of the upper air passages, that is, patients with thrush or bronchitis. From some of these we have been able to isolate fungi, and it would appear that these organisms were related to the disease or were a factor in causing the symptoms. We wish to report here briefly concerning the organisms isolated from these patients and to consider the relationship of the organisms isolated to the particular conditions.

In three cases of mouth infection (thrush) we have found monilia or monilia-like organisms, all of which are in general very similar in form and in cultural qualities. Two of these cultures were obtained from babies in whom there existed quite evident buccal lesions and both cases cleared up quite readily under treatment. In one of these cases the organisms were also present in the stool, and there was associated with the lesions in the mouth a diarrhea which stopped as soon as the oral lesions disappeared. The third patient was an adult and the lesions of the mouth were the only evident symptoms; here also the symptoms cleared quite readily. We could not by studying the growth of the organisms on various simple mediums differentiate between the organisms found in the two cases from the infants and the one found in the adult; the three organisms appeared to be identical or at least closely related. At least temporarily we classify these organisms as monilia.

We have also taken cultures from a number of patients with bronchitis associated with asthma; these were, without exception, cases in which the affection had been of rather long duration and in which no evident causative factor had been determined. We have examined the sputum from fourteen such patients but found the fungi present in only five of the cases examined. In all five of those cases in which fungi were shown to be present, we isolated organisms that were similar to those found in the cases of mouth infection, organisms, therefore, which we, for the present at least, must class as monilia.

Two of these patients were treated with vaccines prepared from the organisms isolated from the particular cases and in both an improvement occurred. One of the cases, however, passed out of our control before a full course of treatment could be completed and, therefore, we are unable to state the final result. In the other patient an almost complete disappearance of the symptoms followed the treatment with the vaccine.

As we have stated above, there was a marked similarity, if not complete identity between the organisms isolated from the patients in whom a mouth infection existed and those isolated from patients who suffered from bronchitis. In all cases, the growth on Sabouraud's medium was creamy white, raised and glistening. In pour plate cultures there appeared mycelial outgrowths with masses of conidia at the

junction of the articles. The reactions in carbohydrate mediums were in general similar but not identical, as shown in the accompanying table.

We do not, at the present time, desire to lay too much stress on the differences noted here in the action of the various strains on carbohydrates. It is possible, and from the reactions recorded in the table seems probable, that we are dealing with different species of monilia; however, it seems quite likely that we deal with a number of closely related species. We find that no two cultures show identical actions on the various carbohydrates and we are in doubt as to how we should interpret these differences in connection with classification of these organisms. At the present time, then, we prefer to group these organisms only as monilia.

Reactions in Carbohydrate Mediums of Organisms Isolated from Patients with Mouth Infection and from Patients with Bronchitis *

Infection of	Culture Number	Milk	Gelatin	Dextrose	Levulose	Galactose	Saccharose	Maltose	Lactose	Inulin	Dextrin
Mouth	117	Alk, Cg	Arb	AG	AG	A	AG	AG	0	A	A
Mouth	118	Alk, Cg	Arb	AG	AG	A	A	AG	0	0	A
Mouth	216	Alk, Cg	Arb	AG	AG	A	A	AG	0	0	AG
Bronchus	150	Alk, Cg	Arb	AG	AG	A	AG	A	0	A	A
Bronchus	166	Alk, Cg	Arb	AG	AG	AG	A	A	0	A	A
Bronchus	215	Alk, Cg	Arb	AG	AG	0	A	A	0	0	AG
Bronchus	220	Alk, Cg	Arb	AG	AG	AG	AG	AG	0	0	A
Bronchus	262	Alk, Cg	Arb	AG	AG	A	AG	AG	0	0	A

* Alk means medium becomes alkaline; Cg, coagulation of casein; Arb, arborescence; A, acid production; G, gas production, and 0, no change.

In no cases were ascospores seen nor morphologic or cultural qualities that would warrant our considering these organisms as belonging to any group other than the fungi imperfecti.

The question that arises in view of these findings and the findings of other investigators is as to the exact relation of these monilia to infections of the upper air passages.

It has been accepted as fact for many years that the causative agent of thrush is a fungus, called by some a monilia, by others oidium and by still others an endomyces. Castellani and Chalmers [4] have stated that thrush may be due to a number of different fungi, and they have noted twelve species of monilia, three species of oidia, a hemispora, willia, endomyces, and possibly some saccharomyces. We should keep in mind that in most cases of thrush the infection is not severe nor does it tend to cause a high mortality; presumably, therefore, we deal with an organism of a low degree of virulence. But the vital point is, on the other hand, that we do accept the fact, and there seems to be ample proof, that these various fungi may be pathogenic agents in the human organism.

4. Castellani and Chalmers (footnote 2, pp. 1741-1744).

At the present time we are studying in this laboratory the pathogenicity of these and similar organisms in rabbits. The experiments so far seem to show that the virulence of different strains of monilia is quite variable and that in general large numbers of organisms must be administered to cause the death of the animals. However, it appears that when these organisms are administered intratracheally they practically always cause the death of the animals, which show at necropsy a pneumonia and a generalized infection with the monilia. It appears then that these organisms are variable in their action, that they are, however, relatively avirulent, but that they may have an affinity for the tissues of the respiratory system.

When then we find similar organisms associated with certain cases of bronchitis or asthma, it appears quite reasonable and quite plausible to assume that here also these organisms may be a factor in the continued irritation and inflammation of the deeper air passages. This assumption has, of course, been accepted by many investigators and fungi have been fairly generally accepted as agents in causing bronchitis. Possibly, the relatively satisfactory results obtained by treatment of some of these cases with an autogenous vaccine may also serve to strengthen the acceptance of the relationship of these organisms.

Granting, however, the likelihood and even accepting as a fact that these fungi do cause bronchitis, we should, in our etiologic study, probably go further than simply accepting this relatively avirulent agent as a causative factor.

We know that in thrush the infection occurs usually in infants and most frequently in undernourished persons. Probably in the great majority of cases the individuals affected, either young or adult, are suffering from some condition that we may say lowers their resistance. We recognize this lowered resistance as a factor in the occurrence of infections in the mouth in which these fungi play a rôle. It would, therefore, appear only reasonable that when similar organisms are found associated with bronchitis and are assumed to be the causative agent, we should, reasoning by analogy, expect that the monilia are not alone as the causative factors, but that other factors, possibly of equal importance, also play a rôle.

We might here call attention to the fact that in two cases of rather advanced tuberculosis (two cases not included in our series here) we were able to demonstrate monilia in the sputum. We believe that in these cases the yeastlike organisms were essentially secondary invaders.

It seems reasonable to assume that the monilia are secondary or concomitant factors, although possibly they may be the chief ones in maintaining the chronicity of the symptoms. It is quite possible that some irritant agent, bacterial, toxic or mechanical, may initiate in the mucosa of the bronchus certain changes, as a result of which the monilia

are now able to grow and to maintain their existence here. If these assumptions are correct, we would have to interpret bronchomoniliasis and probably many types of bronchomycosis as conditions in which a primary factor, either still acting or no longer acting, initiated certain changes that permitted the fungi to gain foothold and to find more or less permanent lodgment in the bronchi; that, however, we must consider the monilia or other fungi as the essential and important elements in maintaining the irritation in these locations. In studying such cases, then, we should as a rule look beyond the relatively avirulent monilia, without in any way ignoring the rôle of these fungi, for some other possible factor in the causation of the chronic inflammation.

CORONARY THROMBOSIS WITH CONGENITAL ABSENCE OF THE LEFT CORONARY ARTERY

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The clinical features of coronary obstruction are fairly generally known. The character and distribution of the pain associated with definite changes in the cardiac findings constitute a clinical picture that is rarely unrecognized by those familiar with the condition. This case is of particular interest because of the congenital absence of the left coronary artery.

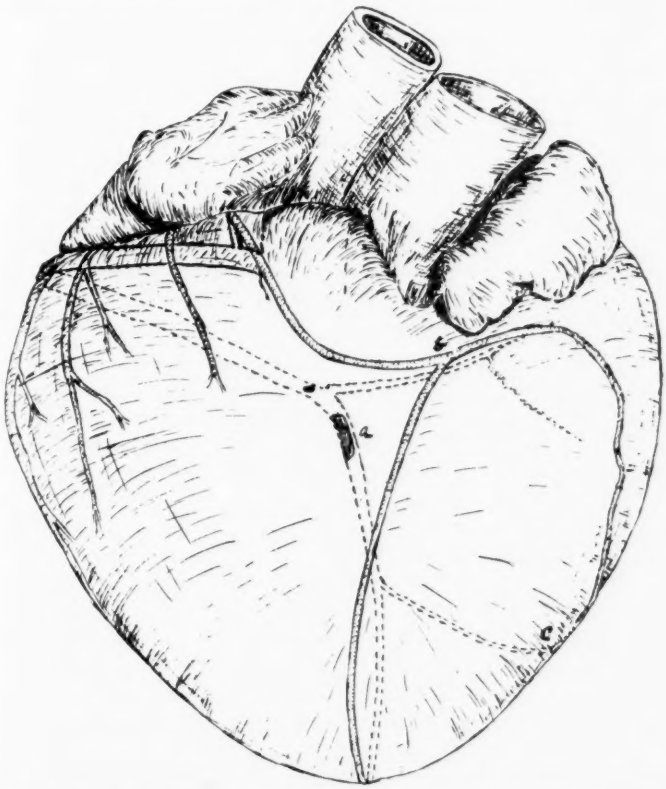
REPORT OF CASE

History.—S. B., a man, aged 46, was admitted to the University Hospital, May 26, 1925. He complained of severe pain over the lower sternal region and shortness of breath. He stated that he had been working in a stone quarry and was obliged to push cars filled with stone. While pushing a car the day prior to entering the hospital, he was suddenly seized by a severe pain over the lower anterior chest which appeared to be beneath the sternum. The pain was so severe that he was compelled to stop work immediately. He was very short of breath and because of dizziness had to lie down. He was, however, unable to lie flat because of the pain and shortness of breath. The distress continued throughout the day and night and was still severe when he was admitted to the hospital.

The past history was essentially negative except for gonorrhea in 1910 and a nocturia for the last five or six years. He stated that he had not had syphilis. It was later discovered, however, that he had been treated for a syphilitic infection. He was a moderate user of tobacco and alcohol. He was married and had three living children. Five died during infancy.

Physical Examination.—The patient was well developed and nourished. He was apparently in great distress and complained of pain over the lower sternal region. He was obliged to sit up because of shortness of breath. The pupils were equal, but reacted rather sluggishly to light. The face, nose and ears were negative. The mucous membrane of the mouth was cyanotic but otherwise normal. The pharynx was slightly congested. There were no scars. The neck was negative for glands and the thyroid was not enlarged. The chest was symmetrical and well developed. The expansion was limited because of pain and dyspnea. The percussion note was slightly impaired at the base and moist râles were heard. The apex impulse was not visible, but was palpated slightly outside and below the nipple. The left border of the cardiac dulness extended 3 cm. beyond the midclavicular line in the fifth interspace. There was no apparent increase in the substernal dulness. The cardiac tones were poorly differentiated and there was a gallop rhythm. The aortic second tone was slightly accentuated. No murmurs were heard. The cardiac rate was 120 per minute and the rhythm was regular. The systolic blood pressure was 90 and the diastolic 68. The pulse volume was small and easily compressed. There was no apparent thickening of the wall of the brachial or radial arteries. The liver was easily palpated and tender. There was no tenderness elsewhere in the abdomen and no tumor masses were felt. The extremities were negative and the reflexes and sensations were intact.

The temperature on admission was 101 F. In the blood count hemoglobin was 85 per cent; red blood cells totaled 4,320,000 and white blood cells 9,000. The urine was negative. An electrocardiogram was taken on the eighth day after admission to the hospital. The amplitude of the Q-R-S group was markedly diminished and the duration increased. The chief ventricular deflection in Lead I was a negative phase. The T-wave was prominent in each lead. In subsequent curves the T deflection became negative and finally returned to the iso-electric phase. There was no further change in the Q-R-S group.



Main surface arteries of the heart: the course of the arteries on the position aspect is represented by interrupted lines; *a*, site of the thrombus; *b* and *c*, location of free anastomosis.

Present Illness.—During the first four days in the hospital the pain was continuous except when relieved by morphine. Thereafter, for the following ten days the distress returned on the slightest exertion. A temperature ranging from 99.2 to 101 persisted for two weeks. On the second day a pericardial friction rub was discovered. The gallop rhythm was a constant finding throughout the period of observation. The systolic blood pressure was never above 100 and on several occasions was below 90. By the end of the second week the shortness of breath had subsided and the signs of passive congestion had disappeared. At the end of two months the patient was allowed to be up in a chair and was gradually per-

mitted to walk. August 2, he was discharged from the hospital. His condition, however, was not satisfactory. During the night he was again seized by severe pain in the chest and he became very dyspneic. He returned to the hospital the following morning in a critical condition with the findings of cardiac failure. He improved somewhat for a time, but later the course was progressively downward and he died, November 22, from cardiac failure. The clinical diagnosis was coronary obstruction and cardiac failure.

Necropsy.—The necropsy findings will be limited to the heart and aorta; the pericardial cavity contained a few centimeters of clear fluid. The pericardium was adherent to the apical region of the heart. The heart was markedly enlarged. The greatest transverse diameter was 17 cm. The heart with the contained blood and the pericardium weighed 930 Gm. The right chambers were more dilated than the left. The thickness of the wall of a large portion of the anterior and lateral aspect of the left ventricle was definitely reduced. Sections of the musculature in this region were largely replaced by fibrous tissue. The endocardium of practically the entire left ventricle was very pale. Both ventricles contained mural thrombi. There was only one coronary artery opening into the aorta (accompanying figure). The artery leading to this opening was unusually large and followed the normal course of the right coronary artery around the auriculoventricular groove posteriorly to the interventricular septum. At this point the artery divided into two branches, the largest of which descended along the interventricular septum and the smaller continued around the auriculoventricular groove to the lateral aspect of the left ventricle. The descending branch was occluded near its origin by a thrombus (*a*). The lateral vessel, after reaching the apex of the heart passed upward along the interventricular septum on the anterior surface to the auriculoventricular groove. Here the vessel joined (*b*) with a fairly large artery coming down over the base of the right ventricle from the first portion of the main coronary artery which continued lateralward over the base of the left ventricle, then downward to the posterior lateral aspect of the left ventricle. At this point (*c*) it anastomosed with a lateral branch of the occluded posterior descending artery. The sclerosis was most extensive in the early portion of the main artery and in some places was calcified. There were no significant changes in the aorta.

COMMENT

In the case herewith reported there were no clinical manifestations of myocardial weakness prior to the cardiac accident. The patient had been doing the heaviest type of physical work without any discomfort whatever. The symptoms typical of coronary thrombosis [1] were the sudden onset of severe substernal pain which lasted for days and was relieved only by the repeated hypodermic administration of morphine, associated with the appearance of the symptoms of cardiac failure, such as marked dyspnea, cyanosis, edema of the lungs and engorgement of the liver; changes in the cardiac findings, such as increase in size, muffled tones, gallop rhythm and later the discovery of a pericardial rub, together with temperature and leukocytosis. The progressive change in the electrocardiogram and the later clinical course further justified the diagnosis.

The anomaly of the coronary circulation was very unusual. The blood supply to the entire heart was furnished by one large artery which

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912; Thrombosis of the Coronary Arteries, J. A. M. A. **72**:387 (Feb. 8) 1919.

during its early course, corresponded in location with that of the right coronary artery. Later branches were given off which reconstructed in a diminutive manner the descending and circumflex branches of the left coronary artery, as shown in the accompanying figure. The differences in the size of these vessels and the usual two main branches of the left coronary artery was striking. The blood supply to the left ventricle was thus apparently much less than in the normal subject. It was difficult to understand how the blood supply to the left ventricle in this instance permitted the individual to perform heavy physical work. It is possible that the blood supply derived directly from the left ventricular cavity might have compensated for the apparent deficiency in the main coronary vessels.[2]

The anastomosis of the arteries which supplied the left ventricle was an interesting featurue. There was a free anastomosis between the two main branches of the posterior descending artery and the branch coming off from the first portion of the main coronary artery which passed lateralward and downward over the basal and lateral aspect of the left ventricle to the posterior surface (*b* and *c*). This extensive anastomosis was undoubtedly a compensatory development following the coronary accident and had reestablished a fairly satisfactory circulation to the infarcted area. Similar compensatory anastomoses[3] have previously been described in man[4] and have been observed experimentally.[5]

It is to be recalled that the sclerosis of the coronary artery was advanced whereas the aorta was regarded as normal. Even though the patient gave a strongly positive Wassermann reaction, the sclerosis corresponded to the senile type. It was considered that perhaps the anomalous coronary circulation was possibly largely responsible for the advanced changes in the vessels. The one vessel from the aorta furnished a pathway for the blood to the entire heart which is ordinarily supplied by two, and in some instances three distinct arteries. This obviously placed an excessive strain on the lone coronary artery.

The area of infarction was confined to the left ventricle and the changes in the electrocardiogram were similar to those produced experimentally by the ligation of branches of the left coronary artery and to those following the occlusion of corresponding arteries in man.[6]

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2. Pratt, F. H.: The Nutrition of the Heart Through the Vessels of Thebesius and the Coronary Veins, Am. J. Physiol. **1**:86, 1898.

3. Cowan and Ritchie: Diseases of the Heart, London, 1922, p. 42.

4. Oberhelman, H. A., and LeCount, E. R.: Variations in the Anastomosis of the Coronary Arteries and Their Sequence, J. A. M. A. **82**:1321 (April 26) 1924.

5. Smith, F. M.: The Action of the Nitrites on the Coronary Circulation, Arch. Int. Med. **28**:836 (Dec.) 1921.

6. Smith, F. M.: The Ligation of the Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918; The Electrocardiographic Changes Following the Occlusion of the Left Coronary Artery, Arch. Int. Med. **32**:497 (Oct.) 1923.

MYCOTIC ANEURYSMS

A REPORT OF TWO CASES *

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The cases in this report are of particular interest because they offer suggestive clinical evidence as to the mechanism of the formation of a mycotic process, and illustrate the probable cause of pain in such a condition. Clinical evidence also suggests that the pathologic process is the same in arteries and veins, and differs only in the end-result.

Mycotic (bacterial) infection of blood vessels may occur as has been discussed by Stengel and Wolferth,[1] as a result of an embolus in the lumen of a vessel, by implantation of infected material on the intima, or through emboli in its vasa vasorum. In favor of the last named mechanism the following cases are offered as suggestive evidence. In both cases there was pain in the region of artery and vein for a period of time before tumefaction appeared. Since it is generally accepted that an embolus in a large blood vessel does not cause pain if there is adequate collateral circulation, it is reasonable to assume that this symptom was probably due to inflammatory reaction in and about the vessel walls. Furthermore, since pain preceded a palpable thrombus in the jugular bulb it is less likely that the process started as the result of a large embolus than that it started with implantation of infected material on the intima, or small emboli in the wall of the vein. This observation leads to the suggestion that the formative mechanism of a mycotic process is identical in artery and vein. The end-result was a patent aneurysm in the artery and thrombosis in the vein due to difference in pressure and rate of flow in arterial and venous systems. Since pain appeared before tumefaction it is unlikely that pressure on surrounding structures was a contributing factor. It is to be noted, furthermore, that the aneurysms and thrombosed veins were situated in regions of lax tissue, where tumor formation would displace rather than compress contiguous structures.

The sequence of events in these cases, namely, pain and then tumefaction, suggests, therefore, that the mechanism of the mycotic process

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1. Stengel, A., and Wolferth, C. C.: Mycotic (Bacterial) Aneurysms of Intravascular Origin, Arch. Int. Med. **31**:527 (April) 1923.

was an inflammatory reaction in and about the vessel wall, due probably to small, infected emboli in the vasa vasorum.

The records of the Lakeside Hospital show a total of 198 aneurysms. Of this number only the two reported in this article can definitely be classed as mycotic in origin. Three others are suspected of such origin, but the evidence is not complete.

Since the report of Stengel and Wolferth cases have been reported as follows:

Reifenstein:[2] Two reported, one of gonococcal and one of pneumococcal origin.

Horsley:[3] An aneurysm of the axillary artery with a blood culture positive for nonhemolytic streptococcus.

Kolin:[4] An aneurysm of the superior mesenteric artery.

Terplan:[5] An aneurysm of the pulmonary artery with a blood culture positive for *Streptococcus viridans.*

Laubry and Bordet:[6] An aneurysm of the ascending aorta.

Farley and Morris:[7] An aneurysm of the femoral artery.

REPORTS OF CASES

CASE 1.—Mycotic aneurysm of the superior mesenteric artery; hemolytic streptococcus septicemia; acute and chronic bacterial endocarditis; mitral insufficiency; acute and chronic myocarditis; infarcts of kidneys; acute meningitis; tertiary syphilis.

History.—J. L., a man, aged 36, was admitted to the Lakeside Hospital, Nov. 22, 1924, with a complaint of pain in the right side of the chest, headache and malaise, and died, April 15, 1925.

About two weeks prior to admission he experienced malaise and a severe right frontal headache, which later became generalized over the entire head. His throat had been sore for two days, and the right ear had ached for two or three days. He also had pain in the right side of the chest which was intermittent in character and accentuated by inspiration. On the day prior to admission he had a chill and a drenching sweat.

The patient had one attack of gonorrheal urethritis, but said that he had not had syphilis. He also had several attacks of tonsillitis and migratory arthritis.

His prior hospital admissions were as follows:

The first admission was from Nov. 19, 1917, to March 3, 1918. A diagnosis of chronic myocarditis and chronic valvular endocarditis with mitral insufficiency was made. Treatment consisted of sedatives, tincture of digitalis and salicylates. There was considerable, but not satisfactory, improvement.

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2. Reifenstein, B. W.: Two Cases of Mycotic Aneurysm, Gonococcal and Pneumococcal in Origin, Am. J. M. Sc. **168**:381 (Sept.) 1924.

3. Horsley, J. S., Jr.: Aneurysm of Axillary Artery, J. A. M. A. **85**:189 (July 18) 1925.

4. Kolin, L.: Aneurysm of Superior Mesenteric Artery, Arch. f. klin. Chir. **123**:684, 1923.

5. Terplan, K.: Mycotic Aneurysm of Pulmonary Artery with Endocarditis of Open Ductus Botalli in Case of Chronic Infectious Endocarditis, Med. Klin. **20**:1331 (Sept. 21) 1924.

6. Laubry, C., and Bordet, F.: Aneurysm of Ascending Aorta with Secondary Endocarditis, Bull. et mém. Soc. Méd. d. hôp de Paris **47**:179 (Feb. 2) 1923.

7. Farley, D. L., and Norris, G. W.: Mycotic Aneurysm of Femoral Artery, Bull. Ayer Clin. Lab. Pennsylvania Hosp. **7**:57, 1922.

The second admission was from Dec. 8, 1921, to Jan. 29, 1922. On this admission the diagnosis made was hemolytic streptococcus septicemia, bronchopneumonia, and the same conditions in the heart as before. A blood culture, December 10, was negative in ninety-six hours, but one taken, December 16, was positive in the same length of time for hemolytic streptococcus. Treatment consisted of salicylates and the routine treatment for pneumonia. There was excellent recovery from the pneumonia, and the heart was not found to differ materially from its prior condition.

The third admission was from June 6, 1922, to July 2, 1922. On this occasion a diagnosis of acute rheumatic fever and chronic valvular endocarditis with mitral insufficiency was made. A blood culture, June 10, was negative in seventy-two hours. Salicylates gave relief from the arthritis, but the heart showed increased size and diminished myocardial reserve. There were no signs of extension of the endocarditis.

Physical Examination.—The patient was severely ill with a temperature of 39.4 C., pulse 95, and respiratory rate 23. There was tenderness to pressure over the entire right side of the face and head, particularly over the mastoid and frontal sinuses. The ears, sinuses, throat and lungs showed no abnormalities. The eye-grounds also were normal. The heart had slight right and left ventricular enlargement. There was a systolic murmur over the apex and aortic region, and systolic and diastolic murmurs were audible in the third intercostal space to the left of the sternum. The blood pressure was 120 maximum systolic, and 70 minimum diastolic. The pulse was irregular and arrhythmic. These physical findings were indicative of insufficiency of the mitral valve, but further interpretations were doubtful. The right knee and ankle were tender to pressure. All reflexes were hyperactive, except the left Achilles, which was hypoactive. The neck was stiff and there was a bilateral Kernig's sign, but there were no other abnormal neurologic signs.

Laboratory Data.—A blood culture, November 25, was positive in seventy-two hours, yielding one colony per cubic centimeter of blood on dextrose, and eight on plain agar. The organisms were gram-negative cocci in pairs and short chains They were not agglutinated by pneumococcus antiserum. Another culture, December 31, was positive in seventy-two hours also, and yielded eighteen and twenty-two colonies per cubic centimeter of blood, about which there was a slight zone of hemolysis. The organisms were gram-negative cocci in chains and were identified as hemolytic streptococcus. Electrocardiograms were made in December, 1921; January, 1922; June, 1922; December, 1924, and January, 1925. It is remarkable that the first and last of these records showed a curious, rhythmic trigeminy of the whole heart determined by discharge of impulses from three separate supraventricular foci. The remaining records revealed normal cardiac mechanism, frequently interrupted by blocked and unblocked auricular ectopic beats. In spite of these profound intra-auricular disturbances the patient never had auricular fibrillation.

The white blood cell count was 18,200 on admission, but later varied from 10,000 to 11,000. The red blood cell count on admission was 4,480,000 and hemoglobin 80 per cent. Before death they were 3,820,000 and 75 per cent respectively. The urine showed little albumin, no hemoglobin, numerous white blood cells at times, a few red blood cells and hyaline, granular and cell casts occasionally. The spinal fluid contained 111 cells, from 70 to 80 per cent of which were polymorphonuclear leukocytes. Gram-positive cocci were found in the smears, but the cultures were negative and the organism could not be identified. The spinal fluid Wassermann reaction was four plus, but a later one was negative. The blood Wassermann reaction was four plus, but a later one was negative also. Over a period of five days the patient was given 135 cc. of antimeningococcic serum intraspinously in doses of from 15 to 30 cc. (November 27 to December 1). There was improvement clinically, and the cell count dropped progressively (93, 16, 7 and 1). There was no bacteriologic proof of the meningitis being

meningococcic in type, but response to the antimeningococcic serum was so excellent that this etiologic agent was suspected.

Subsequent Course.—Fourteen weeks after admission an aneurysm was noted in the region of the superior mesentery artery, about 4 cm. in diameter and about 5 cm. to the left of, and slightly above the level of the umbilicus. There was a marked thrill and a high pitched bruit immediatley over it. With gentle pressure it could be moved laterally across the spine, but not in the longitudinal axis of the body. The patient had complained bitterly of pain in this location for many weeks, but repeated examination did not reveal the aneurysm until the date named.

This sequence of events, namely, a complaint of pain much earlier than the clinical appearance of the aneurysm, is probably significant as to the cause of pain in such a process. It is scarcely conceivable that an aneurysm of this size, and in this position, could produce pain by compression of surrounding structures; furthermore, pain was as prominent a symptom before as it was after the tumor mass was of sufficient size to be palpable. Likewise, stretching of the arterial wall would scarcely account for the pain. A mycotic aneurysm may arise from an infected embolus in the lumen of the artery by implantation of infected material on the intima, or as the result of a weakened arterial wall, due to small emboli in the vasa vasorum. Embolism of a large artery does not cause pain if collateral circulation is adequate, and this symptom arises only after the wall of the artery has been invaded by organisms from the infected embolus. However, emboli in the vasa vasorum of an artery, associated with the resultant degenerative change, would rapidly become a painful process. This mechanism is much more reasonable than simply an embolus in the lumen.

December 12, a small, red indurated area appeared in the skin, at the base of the fifth right metacarpal, which disappeared in a few days and was embolic in nature. On the same day there was a complaint of pain in the right supraclavicular space. There was swelling and tenderness over the external jugular vein which later became frankly thrombosed.

This sequence of events was exactly similar to that described above. In this instance, however, a vein was involved instead of an artery. Pain was the earliest symptom and was indicative of phlebitis and periphlebitis, prior to the formation of the thrombus. A thrombus resulted rather than an aneurysm because of the lower pressure and slower rate of flow in the vein. Petechiae also appeared in the upper aspect of the right anterior triangle of the neck. December 30, there was one petechia on the tongue, and quite a few more had developed on the palmar surfaces of the hands. February 2, following a complaint of pain and tenderness in the left popliteal fossa and an absent pulsation in the anterior tibial artery, an irregular erythematous area, about 6 by 4 cm., appeared on the dorsum of the left foot. This area was exquisitely tender and disappeared in the course of twenty-four hours. This was another embolic phenomenon. March 2, the right small toe became red, swollen and painful but was also hot to touch, so in all probability the condition was arthritic rather than embolic in origin. This conclusion is based on the observation that plugging of an artery by an embolus gives either no change or a reduction of temperature of the parts distal to the obstruction. March 15, petechiae appeared in the conjunctivae, and in the skin over the distal phalanx of the right middle finger.

An attempt was made to combat the septicemia with mercurochrome intravenously. One hundred and sixty cubic centimeters of a 1 per cent solution were given from January 23 to 29 in doses of 30, 25, 25, 40 and 40 cc., or 5-8 mg. per kilogram of body weight. There was no appreciable effect on the temperature or general condition of the patient.

Pathologic Examination.—An incision 20 cm. long was permitted in the abdomen through which the pathologic examination was made. The body was emaciated. There were numerous petechiae beneath the epidermis of the chest, back, palms of the hands and the soft palate and the conjunctivae. Immediately below the incision, slightly above the umbilicus, there was a hard mass in the peritoneal cavity. It was freely movable laterally and upward but not downward.

This mass communicated with the superior mesenteric artery. It was 7.3 cm. long, 5 cm. wide and 3.5 cm. thick. The interior was 6.2 cm. long, 2.1 cm. wide and 2.1 cm. thick. The width of the wall averaged 4 mm. The interior consisted of a thick, laminated clot of blood, adherent to the dilated wall (fig. 1). The organs were removed through the incision in the abdominal wall.

The heart weighed 700 Gm. The parietal pericardium was firmly united to the epicardium throughout the entire surface of the auricle and ventricle by firm, fibrous adhesions. The right auricle contained a few white, fibrous plaques immediately above the anterior leaflet of the tricuspid valve. The tricuspid valve measured 11 cm. in circumference. The right ventricular wall measured 0.5 cm. in thickness. The pulmonary valve was normal and measured 7 cm. in circumference. The left atrium was greatly dilated in contrast to the right atrium, which was only slightly larger than normal. The wall of the left auricle was much thicker than normal and contained white, fibrous plaques. Immediately above the posterior leaflet in the region of the auricular appendage, the endocardial surface contained numerous sessile, papilliform vegetations. They were firmly adherent to the endocardial surface and reddish white. The mitral valve was 11.5 cm. in circumference. The leaflets were firmly fused at their line of closure. Both were considerably thickened. The greatest thickness was at the line of closure, and here were numerous yellowish white vegetations, the largest being the size of a pea. These vegetations were more marked on the aortic leaflets. The chordae tendinae were thickened and shortened. Small hemorrhages were within the vegetations. The aortic valve was thickened at its base. It was 7 cm. in circumference. The suprasigmoid portion of the aorta contained minute patches of light yellow regions in the intima. The coronary arteries were normal. The surfaces made by sectioning the heart muscle contained a few regions of firm, gray, fibrous tissue, with marked congestion of the interstitial vessels interspersed with small hemorrhagic spots.

Anatomic Diagnosis.—There were petechiae of the left visceral pleura and congestion of the lungs; bilateral localized fibrous pleuri'.s; acute vegetative endocarditis; acute myocarditis; hypertrophy of the left auricle; dilatation of the right ventricle; chronic mitral and aortic valvulitis; chronic adhesive pericarditis; chronic passive congestion of the liver; multiple white infarcts and amyloid formation of the spleen; localized perisplenitis; mycotic aneurysm of the superior mesenteric artery; multiple white infarcts of the kidneys; acute glomerulonephritis; emaciation, and petechiae of the chest, back, palms of the hands, soft palate and conjunctivae.

Histologic Diagnosis.—There were congestion and edema of the lungs; acute infectious myocarditis; chronic passive congestion, focal abscesses and slight amyloid infiltration in the liver; chronic lymphadenitis, with amyloid formation of the lymph nodes; amyloid formation and white infarct of the spleen; acute splenitis; perisplenitis; amyloid formation of the suprarenals; white infarct in the kidney; acute infectious glomerulonephritis, and amyloid formation in the kidneys.

Bacteriologic Examination.—No heart's blood was taken because of the limitation of the incision.

Section Through Aneurysm of Mesenteric Artery.—The walls of the artery were greatly changed. The intima was thickened, and there were considerable necrosis and hyalinization. The endothelial lining had broken or disappeared, and there was breaking of the entire structure.

Most of the elastic tissue had been broken, and in the media much of it had disappeared (Weigert's stain). The muscle fibers also were irregular and broken. Much of the media consisted of fibrous tissue. Certain portions near the intima were hyalinized, and took the eosin stain. The adventitia was thick and fibrous as a rule, although it was thicker in certain regions. There was no sclerosis of the walls of the vasa vasorum. There was considerable fat in the adventitia (sudan III stain). There was no thrombosis of the vasa vasorum, but

a few of them had a slight proliferation of endothelial cells into the lumina. No fibrous tissue was about the nerves (Mallory's analine blue and van Gieson's stains). There were no organisms (bacterial stains).

From the appearance of the wall, healing had occurred, and the process was chronic.

The case may be summarized as one of bacterial endocarditis with hemolytic streptococcus septicemia, in proof of which there was a positive blood culture, evidence of endocardial and myocardial involvement, embolic phenomena and a mycotic aneurysm. The endocarditis persisted in a chronic, or subacute form with exacerbations for a period of eight

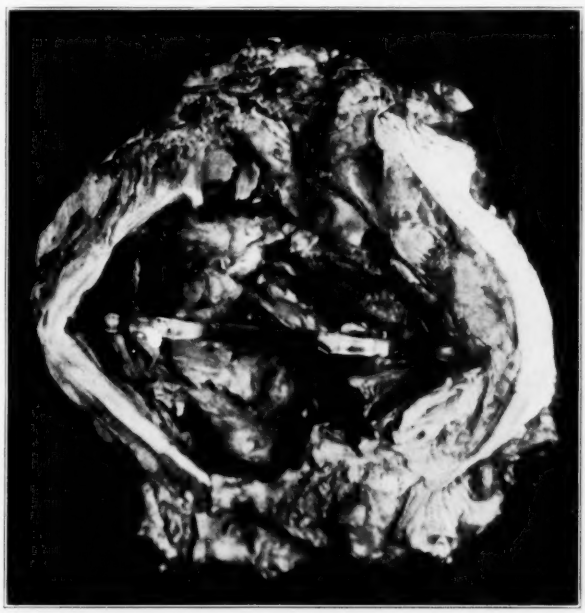

Fig. 1.—Sacculated aneurysm of the superior mesenteric artery with laminated blood clot on the interior and thickened walls.

years. Acute meningitis was diagnosed on the occasion of the patient's last hospitalization, which may have been streptococcic in origin, but seems more plausibly to have been due to the meningococcus because of the clinical reaction to its antiserum. Syphilis was indicated by serologic reactions but nothing was found clinically to confirm it.

The case is reported because of a mycotic aneurysm in the superior mesenteric artery which developed as a part of the cardiovascular disease. It was under close observation for four weeks prior to death, during which time it increased in size and gave rise to severe abdominal pain.

The pathologic examination, however, did not confirm the hypothesis based on clinical findings, that the aneurysm was caused by embolism of the vasa vasorum.

CASE 2.—Mycotic aneurysm of the superior mesenteric artery; streptococcus viridans septicemia; subacute bacterial endocarditis; aortic valvulitis with insufficiency; acute glomerulonephritis; infarct of the spleen.

History.—J. N., a man, aged 25, was admitted to the Lakeside Hospital, April 4, 1925, complaining of severe pain in the left lumbar region; he died, May 20.

About two months prior to admission he was forced to go to bed because of pain in the legs. Shortly afterward his ankles became edematous. About two weeks prior to admission he experienced cramplike pain in the abdomen associated with urination, which was also painful. A few days later he had a twenty-four hour period of anuria. Two days before admission he experienced a severe and persistent knifelike pain in the left lumbar region.

The patient was in the United States navy during the Great War. In 1919, following exposure to wet and cold, he developed an acute migratory arthritis which required hospitalization on shore for about two months. He was told of no cardiac disease before or after this illness, and was returned to active duty. Two years before admission he contracted a gonorrheal urethritis which was properly treated. He was married, and his wife had two children and no miscarriages. Although the patient was conscious of no palpitation of the heart, his wife had noted marked pulsations of the carotid artery for a period of at least two years.

Physical Examination.—The patient appeared extremely ill with a temperature of 39.2 C., pulse 126, and respiration 27. The facies and general attitude betokened severe pain. He assumed all sorts of grotesque positions in bed during attacks of pain, which was localized in the left lumbar region. There was marked pallor but no cyanosis of the skin. There were no petechiae. The precordial activity was markedly increased, and a large excursion was noted in the carotid arteries. There was left ventricular enlargement with a choc-en-dome over the apex in the fifth intercostal space between the left midclavicular and anterior axillary lines. Systolic and diastolic murmurs were heard best in the second intercostal space to the right of the sternum, but the aortic closure sound could be heard, and a diastolic impact was palpable over the aorta. The pulse was celer in type, and a capillary pulse also was observed. The blood pressure was 168 maximum systolic, and 78 minimum diastolic.

These cardiac circulatory findings indicated an insufficiency and possible stenosis of the aortic valve; however, the aortic closure sound and diastolic impact over the aorta implied less insufficiency than the type of pulse, character of enlargement of the heart, and murmur would presuppose.

The splenic edge was firm, tender and palpable 4 cm. below the costal margin. The eye-grounds showed no hemorrhages, but a slight degree of edema of the left disk.

Laboratory Data.—The hemoglobin was 55 per cent, and red blood cell count 3,550,000. The same determinations, eleven days later, were 40 per cent and 2,560,000, respectively. The white blood cell count varied from 17,200 to 7,000. April 27, the blood culture gave no growth in forty-eight hours, but in seventy-two hours a plate gave eight colonies per cubic centimeter of blood, which showed gram-negative cocci in chains. There was no hemolysis. A second blood culture, May 1, gave no growth in twenty-four hours, but in forty-eight hours there were seventeen colonies of a gram-positive coccus in chains and diplo formation. There was no reaction with pneumococcus antiserum. Again, May 19, a culture was positive in seventy-two hours, giving eleven colonies per cubic centimeter of blood on dextrose, and four on plain agar. The organisms were gram-negative cocci in chains, and were identified as *Streptococcus viridans.* The urine was

dark red and smoky, and contained from 1 to 2 Gm. of albumin per liter, hemoglobin, red and white blood cells, and many cellular and granular casts. The blood urea rose from 51 mg. per hundred cubic centimeters on admission to 210 mg. shortly before death. Blood uric acid was from 3 to 4 mg. per hundred cubic centimeters. Roentgen-ray examination of the urinary tract was negative for stones, and the kidneys were not enlarged. The blood Wassermann reaction was negative.

Subsequent Course.—Two weeks after admission an aneurysm was noted in the abdomen, which was about 4 cm. in diameter and could be moved from its position on the left (just lateral to the umbilicus) about 4 cm. to the right, but

Fig. 2.—Vegetations on aortic leaflets; orifice of small mycotic aneurysm of aorta immediately above left posterior leaflet.

not in the longitudinal axis of the body. Pain had been present in this location since admission. The tumor possessed expansile pulsation which could be identified as separated from that of the aorta. At times a thrill was palpable over it, and there was a constant murmur coincident with cardiac systole which could not be heard over either femoral artery.

Petechiae appeared in the mucosa of the mouth and over various parts of the body during the course of the disease. Hemorrhages appeared in the retinae. There was rigidity of the neck and a bilaterally positive Kernig's sign indicating meningitis just prior to death.

Two hundred and twenty-five cubic centimeters of a 1 per cent gentian violet solution was given over a period of ten days, in doses of from 25 to 30 cc. (4 to 5 mg. per kilogram), with no appreciable effect. A blood culture was positive after administration of the dye.

On the morning of his sudden death the patient complained of severe pain over the precordium, but examination revealed no change of physical signs.

Pathologic Examination.—The body was emaciated. The pericardial sac was markedly distended with fluid and clotted blood. There were 400 Gm. of clot and 430 Gm. of serum. This blood was from a small aneurysm 3 cm. in width immediately above the upper edge of the right posterior aortic valve. The aortic valves had numerous vegetations on them. The anterior cusp had a huge vegetation on it 2.1 cm. long, 0.8 cm. wide and 1 cm. thick. It extended on both sides of the leaflets. It was green and red and consisted of numerous small, irregular nodules. The other vegetations were gray and red, and also consisted of numerous small, irregular nodules. They were gray and red

Fig. 3.—Aneurysm of superior mesenteric artery with origin and its relations.

and were not profuse. Vegetations extended into the ring of the aneurysm from the upper surface of the posterior cusp, and they also extended on the posterior surface of the mitral leaflets (fig. 2). The heart weighed 450 Gm. The muscle was dull throughout.

The aneurysm of the superior mesenteric artery began 5.7 cm. from its origin. The opening was well defined but the lower portion of the aneurysm extended in several branches of the artery. It was 5 cm. long and 3 cm. wide. It contained only slightly clotted blood which was easily removed, leaving a clear, gray, smooth surface. The width of the wall was 1 mm. (fig. 3).

The lining of the aorta contained a few small patches of sclerosis.

Anatomic Diagnosis.—There were edema and congestion of the brain; petechiae of the pleura; localized fibrous pleuritis; organizing bronchopneumonia; mycotic aneurysm of the aorta with rupture in the pericardial sac; acute parenchymatous degeneration; "milkpatch" of the pericardium; slight atherosclerosis; sacculated

aneurysm in the superior mesenteric artery; acute splenic tumor; red and white infarcts in the spleen; acute parenchymatous degeneration of the liver; lessened yellow material in the cortices of the suprarenals; acute glomerulonephritis; petechiae in the lining of the stomach; slight localized congestion of the urinary bladder; chronic prostatitis; acute emaciation; missing teeth, and scars of the legs.

Histologic Diagnosis.—There were organizing bronchopneumonia; chronic pleuritis; acute interstitial myocarditis; acute pericarditis; acute periaortitis; red infarct and amyloid formation in the spleen; acute perisplenitis, and acute glomerulonephritis.

Bacteriologic Examination.—No organisms were found in the heart's blood or pericardial fluid.

Aneurysm.—The intima and half of the media were markedly necrotic and stained red with considerable nuclear débris. The débris contained polymorphonuclear leukocytes. In one section there was a definite abscess in the media. Here the adventitia was thin. Bordering this necrotic region the media was fibrous as well as the adventitia. The endothelial lining had disappeared in several sections. The contour of the internal elastic membrane was destroyed and fragments remained. The elastic tissue was broken in certain regions or had disappeared (Weigert's stain). There was a slight amount of fat in the adventitia (Sudan III stain). Compared with the normal aorta bordering the aneurysm, the walls of the aneurysm were thicker. There was no thrombosis of the vasa vasorum, but a few of them contained proliferated endothelium. No fibrous tissue was about the nerves (Mallory's analine blue and van Gieson's stains). No organisms were found (bacterial stains).

Section of the Aorta.—There was marked infiltration with polymorphonuclear leukocytes and pink staining material in the adventitia. The extreme outer surface of the media was involved. This infiltration was especially noticeable about the vasa vasorum.

The process was acute with evidence of healing.

This case may also be summarized as one of bacterial endocarditis with *Streptococcus viridans* septicemia, in proof of which there was a positive blood culture, evidence of endocarditis, embolic phenomena and a mycotic aneurysm.

Historically it would appear that the patient had an attack of rheumatic arthritis five years prior to this hospitalization, at which time he may have developed endocarditis. Whether this attack was an exacerbation of a chronic or subacute endocarditis or a recent and separate process remains a question.

The case is reported because of mycotic aneurysms of the superior mesenteric artery and the aorta. The former developed and progressed in much the same way as in case 1, and the latter ruptured into the pericardial sac. Emboli were not found in the vasa vasorum, but there was an inflammatory reaction about these vessels.

SUMMARY

1. In two cases of mycotic aneurysms each patient had an aneurysm in the superior mesenteric artery, and one in the aorta.

2. One patient also developed a mycotic process (thrombosis) in the jugular bulb.

3. Pain was a prominent symptom before tumefaction appeared, which was suggestive of embolism of the vasa vasorum as the causative factor in both arteries and veins. Pathologic examination, however, did not confirm this clinical hypothesis.

4. In one case the blood culture was positive for hemolytic streptococcus, and in the other for *Streptococcus viridans*.

5. The administration of gentian violet and mercurochrome intravenously did not modify the course of the disease.

GASTRIC ULCER

IV. EXPERIMENTAL PRODUCTION OF GASTRIC ULCER BY LOCAL ANAPHYLAXIS *

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The literature has been saturated with extensive reviews on the etiology and on the experimental production of gastric ulcer.[1] But a painstaking search failed to reveal any work on, or even a direct suggestion of the possibility of, local anaphylaxis as a spontaneous or experimental cause of this lesion.[2] The whole field of local anaphylaxis has attracted but little attention, and almost all the work has been done on the skin.

The pioneer work on cutaneous local anaphylaxis was done in 1903 by Arthus.[3] The phenomenon observed by him was given his name. He reported that if rabbits were injected subcutaneously with a foreign protein at five day intervals the local toxicity of the protein steadily increased. Thus, the first three injections were absorbed rapidly. The fourth induced a soft infiltration which lasted from two to three days. The fifth produced a hard infiltration which remained for five or six days. At the site of the sixth injection, a solid, white caseous mass developed. At the seventh, superficial necrosis terminated in a cuta-

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1. Stewart, M. J.: Etiology of Peptic Ulcer, Brit. M. J. **2**:955-958 (Nov. 24) 1923. Rosenow, E. C.: Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333 (Sept.) 1916. Aschoff, L.: Relations of Mucosal Erosions to the Development of Ulcer of the Stomach, Lectures on Pathology, New York, 1924, p. 279. Ivy, A. C.: Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540-1542 (Dec. 4) 1920. Palier, E.: Etiology of Gastroduodenal Ulcer; Why the Stomach Does Not Digest Itself, New York M. J. **117**:659-662 (June 6) 1923. Ivy, A. C.: Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920. Turck, F. B.: Experimental Studies on Round Ulcer of the Stomach and Duodenum, Illinois M. J. **6**:631-634, 684 (June) 1908. Durante, L.: Trophic Element in Origin of Gastric Ulcer, Surg. Gynec Obst. **22**:399 (April) 1916. Bolton, C.: Ulcer of the Stomach, London, 1913. Rosenow, E. C.: Production of Ulcer of the Stomach by Injection of Streptococci, J. A. M. A. **61**: 1947 (Nov. 29) 1913. Karsner, H. T.: The Pathology of Peptic Ulcer of the Stomach, J. A. M. A. **85**:1376 (Oct. 31) 1925.

2. Hayashi, T.: Experimentelle Beiträge zur Fräge der Ulcusentstehung, Ztschr. f. d. ges. exper. Med. **34**:224-278, 1923.

3. Arthus, M., and Breton, M.: Cutaneous Lesions Produced by the Injection of Horse Serum in a Rabbit Sensitized to This Serum, Compt. rend. Soc. de biol., 1903, p. 1478.

neous ulcer which healed only after several weeks. He further established the fact that the reaction was not a result of the protein injection per se, for only 0.5 cc. of the solution would suffice to give a huge reaction area, and would give a reaction only in specifically sensitized animals. Nonspecific protein injections were without effect. The preliminary sensitization could be effected by any parenteral route. The severity of the local reaction differed with the tissue in which it took place. The skin of the ear, for example, was found to be far less susceptible to local anaphylaxis than was the abdominal wall.[4]

Fig. 1.—Pyloric mucosa of rabbit sensitized to beef protein; precipitin titer of 256,000, three days after local injection; ulcer was 18 by 12 mm.

Nicolle in 1907 established the anaphylactic nature of this local reaction by demonstrating that it could be elicited in an animal sensitized passively.[5] This showed that local anaphylaxis depended on specific substances transmissible in the serum.

Opie exhaustively elaborated this work in the light of modern conceptions of anaphylaxis.[6] He made additional contributions to the

4. Arthus, M.: Repeated Injections of Horse Serum in a Rabbit, Compt. rend. Soc. de biol., 1903, p. 817.

5. Nicolle, M.: Contributions to the Study of the Arthus Phenomenon, Ann. de l'Inst. Pasteur **21**:128, 1907.

6. Opie, E. L.: Inflammatory Reaction of the Immune Animal to Antigen and Its Relation to Antibodies, J. Immunol. **9**:231-245 (July 24) 1924; Relation of Local "Sensitization" to Immunity, ibid. **9**:259-268 (July 24) 1924; Fate of Antigen in an Animal Immunized Against It, J. Exper. Med. **39**:659, 1924; Relation of Antigen to Antibody in Arthus Phenomenon, J. Immunol. **9**:255-257 (July) 1924.

effect that: (1) cutaneous local anaphylaxis was not produced with equal readiness in all species; (2) the severity of the Arthus phenomenon varied directly with the precipitin titer, but that there was not an exact parallel; (3) the reaction depended on the simultaneous presence of antigen and antibody in the tissue; (4) a period of desensitization followed the response to a pure antigen but not to a complex one, and (5) the local reaction protected the animal from a general reaction by limiting the antigen to the site of injection. He gave gross and microscopic descriptions of the pathologic changes that occurred. Significant in relation to our work was his statement that tissues of the internal organs might react to the antigen as did skin. He found that injection

Fig. 2.—Perforated ulcer at pylorus of rabbit sensitized to edestin, precipitin titer of 256,000; the animal died four days after gastric injection and the stomach was examined while the body was still warm.

of specific antigen into the lungs of sensitized animals resulted in a local consolidation.

Auer reported that it was not necessary to inject the specific protein locally in order to obtain a local anaphylactic reaction.[7] If the specific antigen was present in subminimal amounts in the general circulation (intraperitoneal injection) of sensitized animals, a nonspecific irritant could concentrate antigen locally in sufficient amounts to elicit a local gangrene. "A subminimal concentration of antigen for noninflamed sensitized cells became effective for inflamed sensitized cells."

7. Auer, J.: Local Auto-Inoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, J. Exper. Med. **32**:427 (Oct.) 1920.

TABLE 1.—*Egg Albumin as Antigen in Rabbits*

Experiment	Sensitizing Protein	Skin Reaction: Control	Skin Reaction: Specific	Specific Precipitin Titer	Stomach Injected with	Interval	Findings at Sites of Injection
1*	Egg albumin	Ringer's solution —	Egg albumin ++++†	256,000‡	Egg albumin	1 hour	Marked congestion and edema
2	Egg albumin	Ringer's solution —	Egg albumin ++++	256,000	Egg albumin	12 hours	Marked congestion
3	Egg albumin	Horse serum —	Egg albumin ++++	128,000	Egg albumin	24 hours	Congestion with central necrosis
4	Egg albumin	Horse serum —	Egg albumin ++++	128,000	Egg albumin	48 hours	Necrosis
5	Egg albumin	N/125 sodium hydroxide	Egg albumin ++++	128,000	Egg albumin	72 hours	Ulcer, 2 by 2 mm., at pylorus, and 2 by 3 mm. at fundus
6	Egg albumin	N/125 sodium hydroxide	Egg albumin ++++	128,000	Egg albumin	4 days	Ulcer, 3 by 1 mm., at pylorus, and 2 by 3 mm. at fundus
7	Egg albumin	N/60 sodium hydroxide —	Egg albumin ++++	128,000	Egg albumin	6 days	Ulcer at pylorus, 4 by 5 mm.; at fundus, 2 by 1 mm., surrounded by a papillomatous ring
8	Egg albumin	Beef —	Egg albumin ++++	128,000	Egg albumin	9 days	Ulcer at pylorus, 4 by 5 mm.; at fundus, 4 by 4 mm.
9	Egg albumin	Squash —	Egg albumin ++++	128,000	Egg albumin	14 days	Large papilloma at pylorus; small scar at fundus; incision healed
10	Egg albumin	Edestin —	Egg albumin ++++	256,000	Egg albumin	39 days	Ulcer at pylorus, 2 by 1 mm., surrounded by papillomatous ring; papilloma at posterior pylorus; scar at fundus; incision healed
11	Egg albumin	Oats —	Egg albumin ++++	256,000	Egg albumin	60 days	Scar at pylorus; nothing in fundus; incision healed
Controls							
12	Egg albumin	Squash —	Egg albumin ++++	128,000	Beef	1 day	Small area of slight congestion
13	Egg albumin	Edestin —	Egg albumin ++++	128,000	Edestin	4 days	Nothing
14	Egg albumin	Oats —	Egg albumin ++++	256,000	Oats	3 days	Nothing
15	None	.....	Egg albumin —	0	Egg albumin	1 day	Nothing
16	None	.....	Egg albumin —	0	Egg albumin	5 days	Nothing
Passive Transfers							
17	Passively sensitized to egg albumin		Egg albumin +++	16,000	Egg albumin	1 day	Marked congestion
18	Passively sensitized to egg albumin		Egg albumin +++	16,000	Egg albumin	5 days	Firm induration centrally necrotic; ulcer at abdominal incision line
19	Passively sensitized to egg albumin		Egg albumin ++++	32,000	Egg albumin	4 days	Ulcer, 3 by 3 mm., at pylorus; large area of congestion at fundus

† We represent by one plus, slight edema for twenty-four hours; by two plus, greater edema which lasts for five days, but then disappears; by three plus, hard fibrotic induration which lasts for a much longer time; by four plus, necrosis with ulceration.

‡ Nonspecific precipitin titers were all negative.

* Almost all the experiments were done at least in duplicate, but a typical result only is given in the table, as the results in each experiment were practically identical.

An anaphylactic reaction could thus, under proper conditions, be caused by substances that did not of themselves produce anaphylaxis,[8] such as trauma, acid, heat.

TABLE 2.—*Beef Protein as Antigen in Rabbits*

Experiment	Skin Reaction: Control	Skin Reaction: Specific	Specific Precipitin Titer	Stomach Injected with	Interval	Observations at Sites of Injection
20	Oats —	Beef +++	32,000	Beef	1 hour	Congestion and edema
21	Egg albumin —	Beef ++++	128,000	Beef	16 hours	Congestion and edema
22	Horse serum —	Beef +++	32,000	Beef	48 hours	Firm infiltration, 6 by 9 mm.
23	Horse serum —	Beef ++++	128,000	Beef	60 hours	Ulcer, 3 by 4 mm., at pylorus
24	Squash —	Beef ++++	256,000	Beef	72 hours	Ulcer, 8 by 10 mm.
25	Squash —	Beef ++++	128,000	Beef	4 days	Ulcer, 6 by 8 mm.
26	Squash —	Beef ++++	128,000	Beef	5 days	Ulcer, 5 by 4 mm.
27	Edestin —	Beef ++++	128,000	Beef	9 days	Ulcer, 5 by 3 mm.
28	Edestin —	Beef ++++	256,000	Beef	15 days	Small scar at pylorus
	Controls					
1	Egg albumin —	Beef ++++	256,000	Egg albumin	5 days	Nothing
29	Not sensitized		0	Beef	3 days	Nothing
2	Passively sensitized to beef		32,000	Beef	2 days	Ulcer at pylorus, 3 by 3 mm.; large area of congestion at fundus

TABLE 3.—*Edestin as Antigen in Rabbits*

Experiment	Skin Reaction: Control	Skin Reaction: Specific	Specific Precipitin Titer	Stomach Injected with	Interval	Findings at Sites of Injection
52	Squash —	Edestin ++++	16,000	Edestin	12 hours	Congestion
53	Egg albumin —	Edestin +++	16,000	Edestin	1 day	Congestion with central necrosis
54	Egg albumin —	Edestin ++++	128,000	Edestin	36 hours	Congestion with central necrosis
55	Horse serum —	Edestin ++++	128,000	Edestin	4 days	Perforated ulcer, 3 by 2 mm.; large area of congestion
56	Horse serum —	Edestin ++++	64,000	Edestin	6 days	Nodule at fundus; ulcer at pylorus, 2 by 2 mm.
57	Oats —	Edestin ++++	32,000	Edestin	17 days	Hard mass at pylorus, 2 by 1.5 cm.; nothing at fundus-ulcer of incision healed
58	N/60 sodium hydroxide	Edestin ++++	32,000	Edestin	47 days	Nothing in stomach, incision healed
	Controls					
59	N/60 sodium hydroxide	Edestin ++++	32,000	Beef	2 days	Nothing
40	Not sensitized		0	Edestin	2 days	Nothing

Grineff has described a therapy of local anaphylaxis.[9] He found that intravenous injection of small quantities of a foreign protein prevented the subcutaneous reaction to a local injection on the next day.

8. Wells, H. G.: Present Status of Problems of Anaphylaxis, Physiol. Rev. **1**:44-80 (Jan.) 1921.

9. Grineff, D.: L'Anaphylaxie locale est-elle justiciable du procédé des petites doses de Besredka, Compt. rend. Soc. de biol. **72**:974, 1912.

We repeated and confirmed some of Arthus' and Opie's work, and then applied the principle of local anaphylaxis in an attempt at experimental production of gastric ulcer.

METHODS

Since any complete foreign protein molecule soluble in body fluids could serve as an antigen, unless racemized by alkalis,[10] we had a wide choice of materials. Ten protein preparations were used: (1) commercial egg albumin (Merck & Co.); (2) commercial beef protein (Wilson & Co.); (3) commercial horse serum (Eli Lilly & Co.); (4) commercial casein (E. H. Sargent & Co.); (5) commercial hemoglobin (Merck & Co.); (6) commercial tuberculin, old (Parke, Davis & Co.); (7) milk; (8) squash seed globulin; (9) hemp seed edestin, and (10) oat protein.

TABLE 4.—*Other Proteins as Antigens in Rabbits* *

Experiment	Sensitizing Protein	Skin Reaction		Specific Precipitin Titer	Stomach Injected with	Interval	Findings at Sites of Injection
		Control	Specific				
41	Horse serum	Beef —	Horse serum ++++	25,600	Horse serum	4 days	Congestion and induration
42	Horse serum	Egg albumin —	Horse serum ++++	25,600	Horse serum	6 days	Ulcer, 3 by 2 mm.
43	Horse serum	Egg albumin —	Horse serum ++++	25,600	Horse serum	8 days	Ulcer in anterior pylorus, 3 by 2 mm., surrounded by papillomatous ring; papilloma in posterior pylorus
44	Horse serum	Egg albumin —	Horse serum ++++	25,600	Horse serum	22 days	Scar in pylorus, nothing in fundus, incision healed
45	Squash	Beef —	Squash ++++	256,000	Squash	1 hour	Congestion and edema
46	Squash	Beef —	Squash ++++	256,000	Squash	24 hours	Congestion with central necrosis
47	Squash	Edestin —	Squash ++++	256,000	Squash	36 hours	Edema in pylorus, congestion in fundus
48	Squash	Oats —	Squash ++++	256,000	Squash	3 days	Large hard mass in pylorus with central necrosis
49	Oat protein	Egg albumin —	Oats ++	16,000	Oats	2 days	Large area of congestion
50	Oat protein	Egg albumin —	Oats ++++	64,000	Oats	3 days	Ulcer, 3 by 1 mm.
51	Oat protein	Squash —	Oats +++	16,000	Oats	6 days	Necrotic mass, 11 by 9 mm.
52	Oat protein	Squash —	Oats ++++	16,000	Oats	17 days	Nothing
53	Hemoglobin	Horse serum —	Hemoglobin ++++	.....	Hemoglobin	1 day	Congestion
54	Hemoglobin	Horse serum —	Hemoglobin ++++	.....	Hemoglobin	4 days	Ulcer, 2 by 2 mm.
55	Hemoglobin	Squash —	Hemoglobin ++++	.....	Hemoglobin	33 days	Ulcer at fundus, 4 by 3 mm.; induration at pylorus, 2 by 2 mm.; incision healed

* Four rabbits sensitized to milk and seven to casein gave negative results; three rabbits inoculated with tubercle bacilli and injected intragastrically with tuberculin gave negative results.

10. Wells, H. G.: Chemical Aspects of Immunity, Am. Chem. Soc. Monograph Series, Chemical Catalog Company, 1925, p. 52.

Squash seed globulin and edestin were prepared largely after the method described by Abderhalden.[11] The seeds were ground in a mill. The fat was removed by extraction with ligroine. The fat free crushed seeds were then extracted with 4 volumes of 10 per cent sodium chloride solution. To the filtrate, 4 volumes of distilled water previously heated to 65 C. was added. The mixture was slowly cooled to 5 C. The crystalline globulin that separated out on cooling was washed thoroughly with distilled water until salt free, and dried on a Buchner funnel without the use of alcohol-ether.

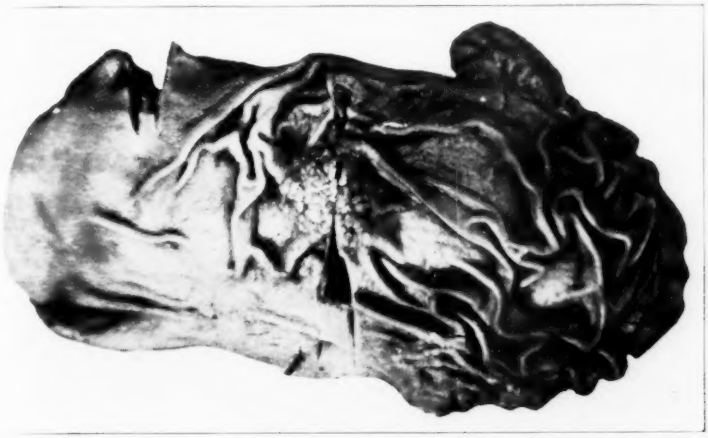

Fig. 3.—Papilloma at site of injection of rabbit sensitized to horse serum, precipitin titer of 128,000, twenty-three days after local injection.

Oat protein was prepared according to the method described by Wells.[12] Ground oats were extracted with 1 per cent potassium hydroxide solution and the filtrate therefrom neutralized with acetic acid. This gave a precipitate, which was washed and dried.

The egg albumin, beef protein and hemoglobin were injected in Ringer's solution. The horse serum, milk and tuberculin were used as such. Casein was dissolved to the extent of 4 per cent in 0.2 per cent sodium carbonate, then diluted with an equal volume of distilled water. This gave a 2 per cent solution of casein in 0.1 per cent sodium carbonate solution which was neutralized to clouding by tenth normal hydrochloric acid. Edestin and squash globulin were dissolved in tenth

11. Abderhalden: Handbuch der Biochem. Arbeitsmethoden, Berlin, **2**:296, 1910.

12. Wells, H. G., and Osborne, T. B.: Biological Reactions of the Vegetable Proteins, J. Infect. Dis. **8**:66-24 (Jan.) 1911.

normal sodium hydroxide solution, diluted five times and neutralized as much as possible. All solutions were made up fresh for every injection.

Pyloric pouches were made in ten dogs according to the method described by one of us.[13] The operation consisted essentially of a resection of the pyloric antrum with a gastroduodenal end-to-side anastomosis. The distal end of the antrum was closed. The open proximal end was sewed into an abdominal wall stab wound so that it opened to the exterior. The Heidenhain fundic pouch also was made. It had already been determined that the simple exposure of the mucosa of the pylorus to the exterior for ten months gave no lesion.

Fig. 4.—Ulcer in pyloric pouch of dog at site of local injection of egg albumin five days before.

In sensitizing rabbits, we resorted at first to Arthus's original method. Two cubic centimeters of the protein solution was injected subcutaneously at five day intervals until a cutaneous ulcer was obtained. Intravenous or intraperitoneal sensitization at different time intervals with different amounts of antigen yielded the same results. Five days after the last subcutaneous injection, the rabbits were placed under light ether anesthesia. By means of a right rectus incision under aseptic conditions, the stomach was exposed. Five-tenths cubic centimeter of the provocative or control dose was then injected through the serosa and the muscularis into the submucosa of the anterior pylorus and anterior fundus. The period of exposure of the stomach was in no case greater

13. Ivy, A. C.: Physiology of Stomach Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

than three minutes and was usually much shorter. Sensitized and nonsensitized rabbits were injected with nonspecific proteins and with the mediums of injection for controls. The incision was sewed up and, at varying intervals after injection, the rabbits were killed and their stomachs examined.

The dogs were usually sensitized by intravenous injection of the protein, but the subcutaneous or intraperitoneal routes gave similar results. Three 5 cc. doses (from 100 to 150 mg. each) were injected on successive days. After from twenty to thirty days, 0.5 cc. of the provocative or control dose was injected into the submucosa of the

Fig. 5.—Ulcer in pyloric pouch of dog at site of local provocative injection of celestin, five days before.

pyloric pouch and into the adjacent skin. Healing time of the ulcers which developed was noted. At varying intervals, the pouch was reinjected. The lesions themselves were then reinjected in an effort to induce chronicity.

To apply Auer's observations to our problem, we reinjected sublethal doses of specific and control antigens intraperitoneally in sensitized dogs. After from thirty to forty-five minutes, a drop of xylene was rubbed on the pyloric mucosa and the reaction observed. The xylene was also applied as a control before reinjection.

To study the effect of gastric motility and acidity on the course of the lesions we placed dogs not previously operated on but sensitized

under morphine-ether anesthesia and aseptically exposed the stomach. The gastric mucosa was exposed by an incision through the anterior gastric wall at the fundus and pylorus. Seventy-five hundredths cubic centimeters of the 2 per cent specific or control solution was then injected into the submucosa of the posterior wall. After different intervals, the dogs were killed and their stomachs examined.

The precipitin titer of the blood was followed in both rabbits and dogs, but satisfactory precipitin changes could be demonstrated only in the rabbits. The titers were run to progressive dilution of antigen by the ring method, in tubes standing for one hour at 37 C.

Fig. 6.—Ulcer at site of injection of mucosa of pyloric pouch of dog three days after local injection with beef protein.

Rabbits and guinea-pigs were inoculated with tubercle bacilli (HR). After three weeks they were given an intracutaneous tuberculin test. After seven days all positives were injected aseptically in the gastric mucosa with old tuberculin.

Passive immunization was effected in rabbits and attempted in dogs. From thirty-six to forty-eight hours after the transfer, the specific antigen was injected into the gastric mucosa of the recipient.

RESULTS

Our preliminary brief repetition of Opie's work on the production of local skin lesions was so corroboratory that a detailed account of these results would be merely a recapitulation of his. All the protein

preparations used, except casein, milk and tuberculin, gave positive results. With only an occasional exception all the animals used gave identical results, and these were characteristic of the species and of the tissue in which the reaction took place. Control injections with nonspecific proteins and with the mediums of solution were, with two exceptions, negative.

Summary of Results in Rabbits.—At the site of injection of the specific protein in the gastric mucosa of sensitized rabbit, there developed an orderly sequence of pathologic changes. For from one to two days there was an extensive area of local passive hyperemia and edema. As this slowly disappeared, the central portion of the area became indurated and necrotic. In from three to six days this area indurated sharply, cleanly and regularly. The margins of the ulcer gradually became thicker, often with mucosal proliferation, and rolled in over the base. Healing was usually complete by twelve days. Rarely did an

TABLE 5.—*Experiments in Guinea-Pigs*

Experiment	Inoculated with	Tuberculin Skin Test Interval		Stomach Injected with	Interval	Findings
1	Tubercle bacilli	21 days	+	Tuberculin	1 day	Slight congestion
2	Tubercle bacilli	21 days	+	Tuberculin	3 days	Nothing
3	Tubercle bacilli	21 days	+	Tuberculin	7 days	Nothing
4	Tubercle bacilli	21 days	+	Tuberculin	8 days	Nothing
5	Tubercle bacilli	21 days	+	Tuberculin	9 days	Nothing
6, 7, 8, 9, 10, 11	Tubercle bacilli	21 days	+	Tuberculin	12 days	Nothing

ulcer remain unhealed much longer. The fundic lesions were practically identical with the pyloric.

Casein and milk gave only a slight congestion and edema which entirely disappeared within five days, or left in its wake only a small firm nodule. The tuberculin injection of the gastric mucosa of tuberculous rabbits and guinea-pigs yielded uniformly negative results. The material was rapidly and uneventfully absorbed (table 5).

Rabbits passively sensitized gave results quite similar to those actively sensitized. In all cases the severity of the cutaneous and gastric reactions varied directly but not exactly with the precipitin titer.

Differences in Tissue Susceptibility in Rabbits and in Dogs.—A significant feature of our results in the rabbit was the difference in severity of response which various tissues of the same animal displayed to the same antigen injected at the same time and precipitin titer. We had repeated Long's work on the testis by injecting the specific protein directly into that organ of a sensitized animal. Whereas the skin over the testis became necrotic and ulcerated, the underlying organ which had received the brunt of the injection was quite unaffected. The opposite testis which had been injected with a nonspecific protein and

the skin over it were entirely unchanged. We found further in rabbits that the gastric reaction was always slightly less severe than the cutaneous. In dogs we found exactly the reverse conditions. The canine skin persisted in giving as a local anaphylactic reaction nothing more than a transient edema. The gastric mucosa injected at the same time with the same dose of antigen gave an intense four plus reaction with necrosis and ulceration.

Summary of Results in Pyloric Pouch Dogs.—Since the reaction in the mucosa could be observed in pyloric pouch dogs ad libitum, the pathologic changes can be more accurately described. Within two minutes after injection of the provocative dose, the pouch contracted violently and everted. The mucosa became blanched, then cyanotic and

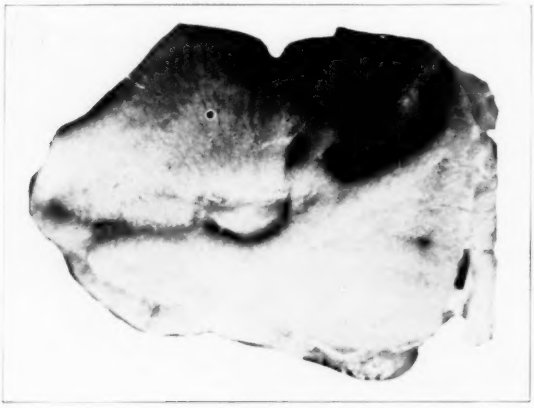

Fig. 7.—Ulcer at pylorus of dog seventeen days after pyloric injection with edestin.

markedly edematous. These last changes were most severe at the area of injection. The dog vomited slightly at the first provocative injection. The next day the pouch as a whole had recovered, but at the site of injection there was a large, bluish black, dried area definitely delimited by a narrow red line of active hyperemia. On the third day the central portion of the area turned grayish yellow. By the sixth day the necrotic mucosa had sloughed out leaving a punched out ulcer with a granulating base. The depth of the lesion varied greatly. The edges and base of the ulcer became firm. The ulcer deepened as the edges increased in thickness and began to roll in toward the base. The base was covered later with a glistening, fragile membrane. The overhanging edges gradually approximated over the much broader base, finally fused and became bound firmly down, leaving a scar. Healing time ranged from twenty-one to thirty days.

The reaction to casein and milk stopped at the stage of cyanosis and edema. The mucosa returned to normal within three days. Injection of the various mediums of solution resulted in no change whatever. Injection of nonspecific proteins yielded no reaction at all, or at most a slight edema and congestion which disappeared within an hour. One small ulcer obtained from a nonspecific protein in a cachectic dog healed rapidly. Further reinjection of the same nonspecific antigen into the same and into other animals produced no reaction whatever. Why it occurred, we cannot explain.

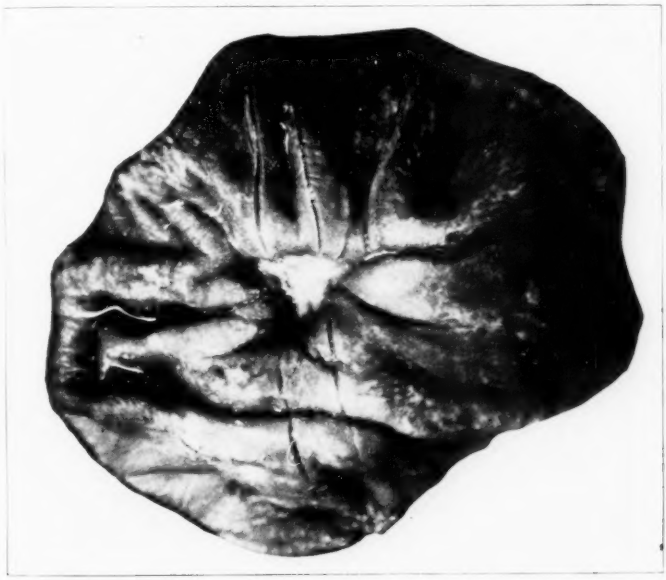

Fig. 8.—Ulcer at site of fundic injection in the same dog as used in figure 7; lines indicate piece removed for microscopic section.

Results Following Repeated Provocative Injections at Various Time Intervals.—If the pouch was reinjected with the specific protein at any time within three days after the first provocative injection, there was no reaction. The skin reaction during this period was also negative or slight. A second injection after three days usually yielded a more or less severe reaction, but after four days always another ulcer. This could be repeated until the pouch was fairly riddled with ulcers.

If the reinjections were made in the base or edge of the ulcers, they extended and became terraced. But these four day reactions became progressively less severe than the preceding ones and healed more

rapidly, so that the total healing time of the original ulcer was not appreciably prolonged. After about five reinjections of the pouch at four day intervals, no reaction at all could be elicited. If this refractory pouch was unmolested for about twelve days, reinjection then yielded another ulcer. If a month or more elapsed between pouch injections, there was no response at all; but hypersensitiveness could be built up again by general or local injections.

In two dogs, a second injection after ten days yielded only a local transient cyanosis but a very severe general reaction. The animals collapsed, went into an extensor spasm, defecated, urinated and vomited;

TABLE 6.—*First Injection in Dogs*

Dog	Specific Protein	Interval	Control Injection		Control Injection		Specific Injection		Healing Time
			Skin	Pylorus	Skin	Pylorus	Skin	Pylorus	
1	Casein	18 days	0.1% $NaCO_3$		Edestin		+	Casein Local cyanosis, edema and discoloration	2 days
			—	—	—	—			
2	Oats	20 days	N/10 sodium hydroxide		Beef		-	Oats Ulcer, 6 by 8 mm.; slight general reaction (vomiting)	23 days
			—	—	—	—			
3	Milk	28 days	Squash		Beef		+	Milk Slight local cyanosis and edema	1 day
			—	—	—	—			
4	Egg albumin	28 days	Ringer's solution		Squash		+	Egg albumin Ulcer, 1.8 by 1.3 mm.; no general reaction	30 days
			—	—	—	—			
5	Edestin	29 days	Squash		Beef		+	Edestin Ulcer, 1.9 by 1.7 mm.; no general reaction	30 days
			—	—	—	—			
8	Beef	22 days	Edestin		Egg albumin		+	Beef Ulcer, 1.5 by 1 mm.; no general reaction	28 days
			—	—	—	—			
9	Squash	32 days	Oats		Egg albumin		+	Squash Ulcer, 1.8 by 1.4 Slight general reaction (vomiting)	30 days
			—	—	—	—			

but in both cases soon recovered. When this was repeated the dogs, despite a polyphagia, went into the condition known as the cachexia of Arthus. This will be repeated on several dogs before we draw any conclusions as to its significance. Opie showed that the local reaction protected the individual from a general reaction by limiting the antigen to the site of the injection.

We had observed in our ulcer rabbits that the incision line invariably became necrotic. This occurred in the passively immunized rabbits also. But in the control gastric injections the abdominal incision lines just as invariably healed perfectly. We extended this observation to the pyloric pouch ulcers, in the light of Auer's conceptions, by the method described above. Intraperitoneal injection of the antigen without the application of

TABLE 7.—*Reinjections of Pylorus at Various Time Intervals in Dogs*

Dog	Specific Protein	Interval	Reaction	Intervals and Reaction
1	Casein	6 days	Dog vomited; local cyanosis and edema; healed in 2 days	1 day, nothing 2 days, nothing 3 days, no vomiting; cyanosis and edema; healed in 2 days
2	Oats	4 days	Slight vomiting; ulcer, 7 by 8 mm.; healed in 20 days	1 day, nothing 21 days, nothing 4 days, nothing
		4 days	Soft infiltration; healed in 3 days	4 days, firm infiltration; healed in 6 days 4 days, firm infiltration; healed in 12 days 4 days, ulcer, 18 by 6 mm.; healed in 20 days
3	Egg albumin	11 days	Severe general reaction; prostration; defecation; vomiting	1 day, nothing 2 days, nothing 3 days, ulcer, 4 by 4 mm.; healed in 10 days
		4 days	Ulcer, 5 by 5 mm.; healed in 10 days	6 days, slight general reaction; ulcer, 2 by 2 mm. 4 days, ulcer, 5 by 6 mm. 4 days, old ulcer, 9 by 6 mm.
		4 days	Old ulcer, 13 by 7 mm.	4 days, older ulcer, 13 by 11 mm. 4 days, old ulcer, 13 by 11 mm.; no reaction 12 days, new ulcer, 11 by 8 mm.
4	Edestin	30 days	Nothing	4 days, nothing 4 days, soft infiltration; healed in 3 days 4 days, firm infiltration; healed in 6 days
		4 days	Hard infiltration; healed in 11 days	4 days, ulcer, 6 by 9 mm. 4 days, old ulcer, 12 by 9 mm. 4 days, new ulcer, 11 by 7 mm.
5	Beef	28 days	Nothing	4 days, nothing 4 days, nothing 4 days, firm infiltration; 5 days
		4 days	Firm infiltration, 10 days	4 days, ulcer, 7 by 6 mm. 4 days, new ulcer, 5 by 5 mm. 4 days, new ulcer, 3 by 4 mm.
		4 days	New ulcer, 2 by 1 mm.	4 days, no lesion 4 days, no lesion 4 days, new ulcer, 6 by 4 mm.
6	Squash	11 days	Severe general reaction; no local	7 days, moderate general reaction; tiny ulcer 4 days, no general ulcer, 10 by 4 mm. 5 days, slight general ulcer, 10 by 7 mm.
		4 days	No general reaction; old ulcer, 10 by 13 mm.	4 days, old ulcer, 10 by 12 mm.; no reaction 12 days, new ulcer, 8 by 5 mm. 12 days, severe general reaction; no local
10	Egg albumin	20 days	Nothing	4 days, nothing 4 days, soft infiltration, 3 days 4 days, firm infiltration, 5 days
		4 days	Firm infiltration, 18 days	4 days, ulcer, 9 by 8 mm. 8 days, moderate general reaction; no local 4 days, ulcer, 6 by 4 mm.

xylene yielded nothing. Together with the application of the irritant to the old lesion, there was an aggravation of the old ulcer to some extent in most cases. The xylene itself had but slight effects. These last results were not sufficiently decisive to be conclusive, though they indicate corroboration of Auer's observations.

The production and course of the local anaphylactic ulcers produced in the gastric mucosa in situ was practically identical with that of the ulcers in the gastric mucosa of pyloric pouches. Healing time was not

TABLE 8.—*Provocative Injection into the Gastric Mucosa in Situ in Dogs Without Pouches*

Dog	Date of Sensitization	Sensitizing Protein	Date of Gastric Injection	Date of Gastric Examination	Findings at Site of Injection
		A. Specific Injections After Intravenous Sensitization			
1	Nov. 26	Egg albumin.....	Dec. 30 (34)*	Jan. 8 (9)	Ulcer in fundus, 7 x 7 mm. Ulcer in pylorus, 5 x 3 mm.
2	Oct. 23	Egg albumin.....	Nov. 17 (25)	Dec. 17 (30)	Scar in fundus Scar in pylorus
3	Nov. 26	Beef protein.....	Dec. 30 (34)	Jan. 8 (9)	Indurated mass in fundus Indurated mass in pylorus
4	July 29	Oat protein ..	Aug. 17 (19)	Sept. 14 (28)	Scar at pylorus Ulcer at fundus, 3 x 3 mm.
5	Nov. 20	Horse serum.....	Dec. 11 (21)	Dec. 20 (9)	Ulcer at fundus, 4 x 8 mm. Ulcer in pylorus, 4 x 6 mm.
6	July 24	Horse serum.....	Aug. 18 (25)	Sept. 2 (15)	Ulcer in fundus Ulcer in pylorus
7	Nov. 26	Edestin.....	Dec. 26 (30)	Jan. 2 (7)	Indurated mass in pylorus Indurated mass in fundus
8	July 24	Edestin.....	Aug. 17 (24)	Sept. 2 (16)	Ulcer in pylorus, 8 x 4 mm. Ulcer in fundus, 6 x 6 mm.
9	July 29	Squash.....	Aug. 22 (22)	Sept. 29 (40)	Scar at pylorus Scar at fundus
10	Dec. 1	Squash.....	Dec. 28 (28)	Jan. 12 (15)	Ulcer in pylorus, 3 x 1 mm. Ulcer in fundus, 7 x 5 mm.
		B. Specific Injections After Sensitization by Other Routes			
11	Oct. 23	Egg albumin subcutaneously	Nov. 20 (27)	Dec. 20 (30)*	Scar in fundus Scar in pylorus
12	Nov. 3	Horse serum subcutaneously	Nov. 24 (21)	Dec. 20 (26)	Scar in fundus Scar in pylorus
13	Nov. 26	Squash intraperitoneally	Dec. 28 (32)	Jan. 2 (5)	Ulcer in pylorus, 12 x 7 mm. Ulcer in fundus, 15 x 9 mm.
14	Nov. 26	Edestin intraperitoneally	Dec. 28 (32)	Jan. 5 (8)	Indurated mass infundus Indurated mass in pylorus
15	Nov. 26	Beef protein	Dec. 23 (27)	Dec. 31 (8)	Nothing in pylorus Nothing in fundus

* The figures in parentheses represent the interval in days since the preceding date in the table.

affected by the acid, the motility or whatever other factors were acting in the stomachs of these dogs.

The ulcers in the fundus were essentially identical with those in the pylorus. Any parenteral route was effective in sensitization. Not all the dogs were equally susceptible to sensitization. It should be noted that dogs 3, 7 and 14 gave only a three plus reaction, dog 15 none at all.

One defective result in our control injections was described above. The only other one occurred in control series A, table 9. A dog that had not been sensitized by us received a gastric injection of squash

seed globulin. An ulcer developed in the pylorus and in the fundus. The animal may have been spontaneously or artificially sensitized before. We cannot vouch for this. The control was repeated on four more dogs with negative results.

All our attempts to find precipitins in sensitized dog's serum by specific precipitation failed. We then made two attempts, one for beef protein and one for egg albumin, to demonstrate that the substances responsible for the local reaction were transmissible in the dog's serum. Three hundred cubic centimeters of whole blood was transferred by Kimpton-Brown-Percy tube from an animal that had been sensitized

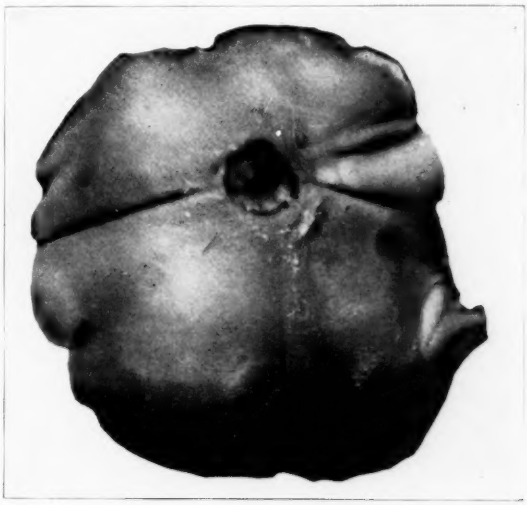

Fig. 9.—Stomach of dog twenty-eight days after injection with oat protein; ulcer, at site of fundic injection, is 4 by 4 mm.

twenty-eight days before to an unsensitized animal. Forty-eight hours later, the recipient received a specific gastric injection which was uneventfully absorbed. A week later, the donor received a specific gastric injection which resulted in the usual ulcer at the pylorus and at the fundus.

COMMENT

The mechanism of local anaphylaxis is discussed in sufficient detail.[14] There is no indication that gastric local anaphylaxis differs essentially

14. Wells (footnote 10). Opie (footnote 6). Kolmer, J. A.: Mechanism and Clinical Significance of Anaphylactic and Pseudoanaphylactic Skin Reactions, Bull. Johns Hopkins Hosp. **28**:163 (May) 1917. Coca, A. F.: Mechanism of Anaphylaxis Reaction in the Rabbit, J. Immunol. **4**:219 (July) 1919. Weil, R.: J. Immunol. **1**:19 (Feb.) 1916.

from cutaneous local anaphylaxis. That our gastric reaction, like the skin reaction, is truly anaphylactic has been proved by conformity with most of Well's criteria: (1) The toxicity of the injected material depends on sensitization of the animal—that is, these substances do not give similar symptoms in nonsensitized animals; (2) the symptoms are characteristic of typical soluble protein reactions, being the same for all the antigens with the same animal, but characteristic of the species; (3) the serum of sensitized animals effects passive sensitization; (4) desensitization follows recovery, and (5) specific precipitins have been demonstrated in the blood of sensitized rabbits.

TABLE 9.—*Control of Injections into the Gastric Mucosa in Situ in Dogs Without Pouches*

A. Lesion Not Appearing in Absence of Previous Sensitization

Dog	Sensitization	Date of Gastric Injection	Gastric Injection	Date of Gastric Examination	Findings at Sites of Injection
16	None	Oct. 23	Egg albumin	Oct. 27 (4)*	Nothing in pylorus or fundus
17	None	Nov. 3	Horse serum	Nov. 6 (3)	Nothing in pylorus or fundus
18	None	Oct. 27	Beef protein	Nov. 1 (5)	Nothing in pylorus or fundus
19	None	Oct. 27	Edestin	Nov 1 (5)	Nothing in pylorus or fundus
20	None	Nov. 10	Squash	Nov. 12 (2)	Nothing in pylorus or fundus

B. Reaction Required a Specific Sensitization

Dog	Date of Sensitization	Sensitization	Date of Gastric Injection	Gastric Injection	Date of Gastric Examination	Findings at Sites of Injection
21	Oct. 23	Egg albumin	Nov. 17 (25)*	Beef protein	Nov. 20 (3)*	Nothing in pylorus or fundus
22	Nov. 3	Horse serum	Nov. 24 (21)	Egg albumin	Nov. 27 (3)	Nothing in pylorus or fundus
23	Nov. 26	Beef protein	Dec. 23 (27)	Horse serum	Dec. 28 (5)	Nothing in pylorus or fundus
24	Nov. 26	Edestin	Dec 28 (32)	Squash	Dec. 31 (3)	Nothing in pylorus or fundus
25	Nov. 26	Squash	Dec. 26 (30)	Edestin	Dec. 28 (2)	Nothing in pylorus or fundus

* The figures in parentheses represent the interval in days since preceding date in table.

The failure to demonstrate satisfactory precipitin titer changes in dog's blood does not prove that their gastric hypersusceptibility is not anaphylactic. The antibody may be so fixed in the tissue that the quantity in the serum is not comparable with that in the tissue. Tissue immunity is not always parallel with serum antibody immunity.

The negative tuberculin results may be ascribed (1) to the use of an anesthetic during the administration of the provocative dose, (2) to a tissue peculiarity, for tuberculin gives a huge reaction in the testis, and (3) to the fact that the animals were sensitized to tubercle bacilli, not to tuberculin. Though the Arthus phenomenon resembles the tuberculin reaction in some ways, Long [15] distinguishes rigidly between local anaphylaxis and hypersensitiveness to infection. Hypersensitive-

15. Long, E. R., and Seyfarth, M.: The Testicle as an Indicator of Allergy in the Hypersensitiveness of Infection and Anaphylaxis, Am. Rev. Tuberc. **9**: 259 (May) 1924.

ness to tuberculin does not protect against tubercle bacilli [16] as it would if tuberculin were a true specific antigen, and if the reaction were truly anaphylactic. The gastric tuberculin reaction in rabbits is comparable only to the skin reaction, but not to the testicular.

The negative casein results support the doubt cast by Seibert [17] on the antigenic power of this protein.

Application of Local Anaphylaxis to the Etiology of Gastric Ulcer in Man.—Gastric ulcer displays several striking etiologic phenomena: (1) The patient frequently is held to suffer from a general susceptibility to gastric ulcers, because the ulcers recur, extend and perhaps multiply—they appear in the absence of any demonstrable local cause; (2)

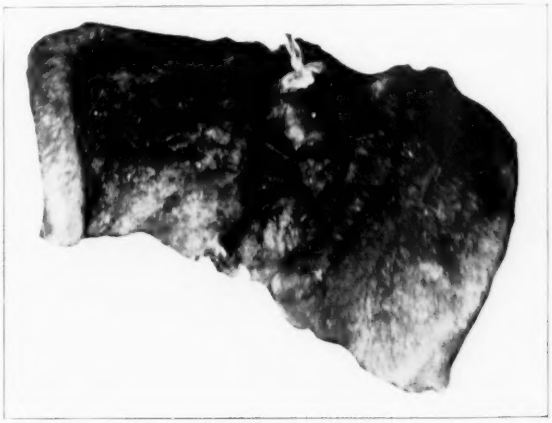

Fig. 10.—Stomach of dog sensitized to horse serum seventeen days after local injection showing ulcer at pylorus.

with acid playing on the entire gastric mucosa only a slight area ulcerates; (3) the field of attack is almost exclusively localized to the pyloric antrum and duodenal cap, and (4) the lesions are acute and chronic.

These phenomena may be more or less closely simulated in the spontaneous production of ulcers by local anaphylaxis, provided our observations are applicable to man. That man becomes generally sensitive to foreign proteins is common knowledge. The specific protein is rubbed into the gastric mucosa. A local reaction arises at the site of this spontaneous specific injection, just as it arises in the diagnostic skin test for protein sensitization. But the gastro-intestinal mucosa reacts

16. Austrian, C. R.: Effect of Hypersensitiveness to Tuberculin upon Subsequent Injection of Tubercle Bacilli, Bull. Johns Hopkins Hosp. **24**:11-25, 1913.

17. Seibert, F. B., and Mendel, L. B.: Protein Fevers, Am. J. Physiol. **67**: 105 (Dec.) 1903.

much more violently than does the skin, and instead of a little red wheal, necrosis and an ulcer develop. This may occur in the absence of any general symptoms. The local response protects the patient from a general reaction by limiting the antigen to the site of injection. After a period of desensitization, reinjection into the edges or base of the ulcer causes lateral extension or perforation. Reinjection into the vicinity produces a second ulcer.

The localization of the lesion in the pyloric ring region may be explained on the basis of the special mechanical and chemical conditions there prevailing. Beyond the duodenal cap, tryptic digestion and alkali racemization diminish or abolish antigenic powers of the proteins.

Fig. 11.—Ulcer at fundus in stomach shown in figure 10; photograph blurred by shrinking of specimen during exposure; specimen preserved in Kaiserling's solution.

The digesting fundus of the stomach is comparatively atonic. The chances for rubbing protein in are therefore slight. At the pyloric ring, on the other hand, the proteins are still antigenic and can be readily rubbed into the mucosa by reason of the high motility, the spasms and the traumatism to which this region is subject.

Chronicity may be established in man by a repetition of local reactions until an irrevocable fibrosis develops. In the presence of specific antigen in the blood, coarse foods, hot drinks, acids and other nonspecific irritants may suffice to elicit these local reactions, by locally concentrating antigen. Once a raw surface is made by an acute local anaphylactic reaction, direct acid digestion thereof may favor chronicity. Our observations support none of these factors in chronicity. We have produced acute lesions that heal slowly, but we have not satisfactorily demonstrated the chronicity of local anaphylactic ulcers in dogs.

How man would react we cannot say. Pribram has started treatment of gastric and duodenal ulcers by intravenous injection of a nonspecific protein [18] (a water soluble plant albumin that he calls "novo-protin"). He gives doses of from 0.2 to 1 cc. at three to four day intervals for about a month. He reports from 50 to 70 per cent good results. Injection is attended at first by a general reaction, a diagnostic local reaction,[19] and an acute exacerbation of ulcer symptoms, later by healing. Hampel and Perutz insist that it be tried in every case of gastric ulcer before considering operative measures.[20]

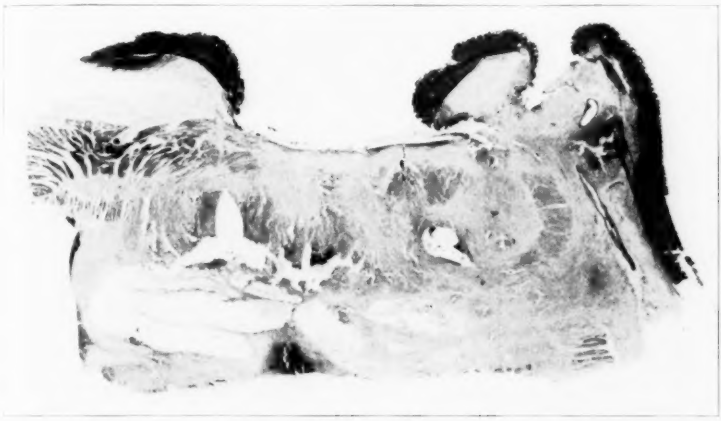

Fig. 12.—Section through ulcer shown in figure 7 (×5); examination at a higher magnification shows a mild inflammatory reaction in and about the base of the ulcer; the connective tissue proliferation should be noted.

SUMMARY AND CONCLUSIONS

1. Acute gastric ulcers were experimentally produced on the basis of local anaphylaxis to specific antigens. Passively immunized animals yielded the same gastric lesions.

2. Healing time of the acute ulcers in rabbits was about twelve days, one not being healed at thirty-three days, and in dogs from about twenty-one to thirty days, one not being healed at thirty days. This demonstrates that these ulcers appear to become chronic in some instances.

18. Pribram, B. O.: Parenteral Protein-Irritation Therapy of Gastric and Duodenal Ulcers, Med. Klin. **30**:958-960 (July 23) 1922.

19. Weiss: Diagnosis of Peptic Ulcer with Protein Injections, Deutsche med. Wchnschr. **49**:1110 (Aug. 24) 1923.

20. Hampel: Med. Klin. **19**:781-816 (June 10) 1923. Perutz: München. med. Wchnschr. **70**:1527-1528 (Dec. 28) 1923.

3. A period of desensitization followed production of the acute lesion. After this period, reinjection yielded another ulcer or caused extension of the first. This was repeated until the mucosa was riddled with ulcers or was occupied by a single large ulcer. Continued reinjection of the ulcer at from three to five day intervals progressively desensitized the dog while it slightly delayed healing of the original lesion.

4. The local reaction limited the antigen to the site of injection, thus preventing a general reaction. Diminution of the local reaction was associated with an increase in the general reaction. Both local and general hypersensitiveness gradually diminished with time, but could be again elicited by local or general reinjection.

5. The anaphylactic nature of the local gastric reaction, like that of the cutaneous, has been established in rabbits. In rabbits the severity of the gastric reaction has been shown to parallel the precipitin titer of the serum. Our data has conformed with most of Well's criteria for anaphylaxis.

6. Precipitins to plant or to animal proteins could not be detected in sensitized dogs' serums.

7. The severity of the local reaction was characteristic of the particular tissue in which it occurred, and of the species of animal involved. Wide differences were observed here. In dogs the gastric reaction was more severe than the cutaneous; in rabbits the cutaneous reaction was more severe than the gastric.

8. Ulcers produced in the fundus were practically identical with those in the pylorus.

9. Motility and other intragastric factors had no effect on the healing time of these ulcers.

10. Positive results were obtained in rabbits and dogs with egg albumin, beef protein, oat protein, squash seed globulin, edestin, hemoglobin and horse serum; negative results with casein, milk and tuberculin.

11. Controls to the mediums of injection and to nonspecific proteins were negative.[21]

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21. At the conclusion of our work a reference appeared in the *Journal of the American Medical Association* to some work by M. Loeper and G. Marchal on "local anaphylactic ulcers" (Effect of Sugar on the Stomach, Bull. Soc. méd. d. hôp. de Paris **49**:721-771 [May] 1925). The original article, like that of Hayashi, revealed no relation at all to anaphylaxis, but again showed simply a matter of drug hypersensitiveness. They had observed simply that the gastric mucosa of certain persons was particularly susceptible to ulceration following the administration of acetyl salicylic acid and antipyrine. They found that the simultaneous administration of sugar prevented the formation of gastric lesions.

THE UNITARY NATURE OF IMPAIRMENT OF RENAL FUNCTION *

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Nearly a century has elapsed since Richard Bright made his celebrated "statements and conjectures regarding the dependence of a peculiar class of Dropsies on disease and irritation of the Kidneys." [1] Since then numerous additions have been made to our knowledge of the symptomatology of Bright's disease, the most significant, perhaps, being arterial hypertension, albuminuric retinitis, and the so-called uremic phenomena largely involving the central nervous system. The systemic manifestations of kidney disease are so variegated, and their association with one another so inconstant, that it was early realized they could not all be due to the same pathogenetic factor. In attempts to explain the connection between the kidney lesions and the associated systemic phenomena, two main paths have been pursued:

1. The study of extrarenal factors. This dates back to the classic investigations of Gull and Sutton [2] on cardiac hypertrophy and Cohnheim and Lichtheim [3] on edema. In the case of uremia, the pathogenetic significance of extrarenal moments has been emphasized only comparatively recently, particularly by Vaquez [4] and Volhard.[5]

2. The introduction of the concept of isolated injury to individual functions of the kidney, the so-called "partial functions," while the other excretory functions are satisfactorily performed, leading to selective retention. This conception was inaugurated by Widal [6] and Strauss [7] in 1902. They found that in uremia there is deficient excretion of the nonprotein nitrogenous constituents of the blood, while in edema sodium chloride is not adequately eliminated. As a result of these studies there arose the division, on a functional basis, of the various forms of Bright's disease into two great groups: (1) the cases in which sodium chloride

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* From the medical division of the Montefiore Hospital.

1. Bright: Reports of Medical Cases, London, 1827, preface, p. viii.

2. Gull and Sutton: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease, Tr. Med.-Chir. Soc. **55**:273, 1872.

3. Cohnheim and Lichtheim: Ueber Hydraemie und hydraemisches Oedem, Virchows Arch. f. path. Anat. **69**:106, 1877.

4. Vaquez: Maladies du Coeur, Paris, 1921, p. 498.

5. Volhard; Mohr, and Staehelin: Handbuch der inneren Medizin, Berlin, **3**:1314, 1918.

6. Widal and Javal: La dissociation de la perméabilité du rein pour le chlorure de sodium et l'urée dans le mal de Bright, Compt. rend. Soc. de biol. **55**:1639, 1903.

7. Strauss: Die chronischen Nierenentzuendungen in ihrer Einwirkung auf die Blutfluessigkeit, Berlin, 1902.

is retained, clinically characterized by edema, and (2) the group in which nitrogenous bodies are retained, showing a tendency to uremia. This subdivision has found wide favor, the two groups being known in this country as nitrogen retaining and chloride retaining, in France as uremigenic and hydropigenic, and in Germany as hypazoturic and hypochloruric. It is everywhere recognized that combinations of the two types are very common. Further study [8] of the nitrogen retaining type in this country has led to the claim that as the kidney fails impairment of excretion of the individual nonprotein nitrogenous constituents of the blood occurs at successive periods, the first retained being uric acid, next urea, and finally creatinine.

In this article we desire to present evidence that, no matter what its anatomic substratum, impairment of renal function is manifested by injury to *all* the excretory functions of the kidney, and that when selective retention occurs in Bright's disease, it is not due to inability of the kidney to excrete the retained substance, but to intervention of an extrarenal factor.

BLOOD CHEMISTRY IN UREMIA

It was mentioned in the foregoing that the differentiation of the nitrogen retaining form of kidney disease dates from the demonstration by Widal and Strauss that the concentration of nonprotein nitrogen in the blood is increased in uremia. In these cases the chloride content of the blood was shown to be normal. These researches furnished the chemical explanation of von Koranyi's [9] earlier finding that in uremia the freezing point of the blood serum is lower than normal, but that the conductivity of the serum is normal; i. e., that the total molecular concentration is increased but not the concentration of the electrolytes. At the time only nonprotein nitrogen, urea and chloride could be determined accurately in the small quantities of blood available clinically. Since then methods have been developed, particularly in this country, for the estimation of numerous other substances in small volumes of blood. With these micromethods blood chemistry in uremia has been exhaustively studied and the following findings relevant to the present topic may be taken as definitely established:

The nitrogenous bodies urea, uric acid and creatinine are increased in the blood in true uremia. It has been stated [8] that uric acid accumulates before the others. However, isolated increase in the uric acid content of the blood in the presence of normal urea values in a hypertensive patient

8. Myers, V. C.; Fine, M. S., and Lough, W. G.: The Significance of the Uric Acid, Urea and Creatinine of the Blood in Nephritis, Arch. Int. Med. **17**:570 (April) 1916.

9. Von Koranyi: Physiologische und klinische Untersuchungen über den osmotischen Druck thierischer Fluessigkeiten, Ztschr. f. klin. Med. **33**:1, 1897; **34**:1, 1898.

is not due to renal failure but is a metabolic phenomenon correlated with the hypertension.[10] Such hyperuricemia cannot, therefore, be considered as an example of selective retention.

Indican, phenol, and aromatic oxyacids[11] are found in increased concentration in the serum in renal failure. Indican, the best studied, may accumulate to a concentration of 1 mg. per hundred cubic centimeters, the normal being about 0.05 mg. per hundred cubic centimeters. Its amount, however, varies greatly, due to alterations in the source of supply (intestinal putrefaction).

The phosphate content of the serum may be increased to over ten times the normal.

The sulphate concentration of the serum may be increased to over twenty times the normal.[12]

Potassium is only moderately increased; the highest figure I have seen in the literature is 36 mg. per hundred cubic centimeters,[13] the normal being 20 mg.

TABLE 1.—*Blood Chemistry in Uremia*

Increased		Not Increased	
Urea	Phosphate	Chloride	Calcium
Uric acid	Sulphate	Sodium	Water
Creatinine	Urochromogen	Magnesium	Ammonium (discussed in text)
Indican	Potassium (slightly)		

Urochromogen retention in the serum has been demonstrated by Becher,[11] thus explaining the light color of the urine even in the absence of polyuria.

The urinary constituents, chloride, sodium, magnesium, calcium and water, are not increased in the blood in uremia; in fact, chloride and calcium are often present in subnormal concentrations. Water is not retained as a result of renal insufficiency per se (discussed later), and therefore belongs in this group, though we are not accustomed to speaking of it in terms of "concentration."

From the standpoint of blood chemistry, then, the urinary constituents may be divided into the two groups given in table 1, the criterion being whether or not their concentration in the blood is increased when the kidney fails.

10. Fishberg, A. M.: The Interpretation of Increased Blood Uric Acid in Hypertension, Arch. Int. Med. **34**:503 (Oct.) 1924.

11. Becher, E.: Studien über Chromogene in Serum und Harn von Nierenkranken, Deutsches Arch. f. klin. Med. **148**:46 (July) 1925.

12. Denis, W., and Hobson, S.: A Study of the Inorganic Constituents of the Blood Serum in Nephritis, J. Biol. Chem. **55**:183 (Feb.) 1923.

13. Briggs, A. P.: A Study of the Inorganic Elements of the Blood Plasma, J. Biol. Chem. **57**:351 (Sept.) 1923.

The chemical composition of the blood thus resulting constitutes the "chemical blood picture" of renal insufficiency. What is the reason that certain urinary constituents increase in the blood in renal insufficiency, while others do not? The following explanations are widely held:

1. The explanation generally advanced is that only certain functions of the kidney involving the excretion of the substances accumulating in the blood are injured, while the power of the kidney to eliminate the bodies present in normal concentration is unimpaired. It will be shown shortly that this opinion is fallacious and that when renal function is impaired *all* the excretory functions of the kidney are injured.

2. It may be thought that those substances whose concentration in the blood in renal insufficiency is not increased are really retained, but that they are stored in the tissues and not in the blood. In the case of sodium chloride, this is often presumed to lead to a secondary retention of water with the formation of edema. But as most cases of uremia in chronic Bright's disease show no edema whatsoever, or merely an obviously "cardiac" edema, and often the tissues are plainly dehydrated, it has been assumed that sodium chloride may be retained in the tissues without corresponding retention of water, the rétention sèche (dry retention) of Ambard and Beaujard.[14] But that *actual retention of chloride in noncdematous patients is manifested by a rise in the chloride concentration of the blood* is shown by instances of complete or almost complete anuria due to mechanical obstruction of the urinary passages in which the patient continues to ingest chloride as usual. In such cases of mechanical anuria, in which chloride continues to be ingested, we often see the blood chloride concentration rise to very considerable heights. Thus, in a case of carcinomatous obstruction of both ureters the plasma chloride concentration rose to 1,100 mg. per hundred cubic centimeters (as sodium chloride) in a case of cystitis and ureteritis following a spinal cord lesion to 950 mg., and in a patient in whom the ureters had been implanted in the abdominal wall and then become obstructed to 738 mg. Similar instances have been published by Braasch[15] and others; in one of Braasch's cases the plasma chloride attained the enormous height of 1,500 mg. per hundred cubic centimeters.

There seems to be no reason for believing that retention caused by mechanical blockage of the urinary passages affects the concentration of a substance in the blood differently than does an equal retention due to disease of the kidney itself. We would, therefore, expect that if chloride were retained in Bright's disease to the same extent as in these cases of mechanically caused anuria the concentration of chloride in the blood

14. Ambard and Beaujard: La rétention chlorurée sèche, Semana méd., 1905, p. 133.

15. Braasch: Ueber die klinischen Erscheinungen bei langdlauerender Anurie, Deutsches Arch. f. klin. Med. **103**:488 1911.

would rise as it does in the anuria of obstruction. The fact that in uremia terminating chronic Bright's disease the concentration of chloride in the blood is not increased, but in fact often decreased, speaks strongly against the existence of chloride retention in these nonedematous uremic patients.

It thus seems clear that neither selective injury to individual functions of the kidney nor extravascular storage in the tissues explains the chemical picture of the blood in uremia, in which certain substances, e. g., urea, accumulate, while others, such as chloride, do not increase in concentration. The explanation, we believe, is purely quantitative. In the quantitative study of renal insufficiency three factors must be considered:

1. The concentration ratios of the individual urinary constituents.

2. The possibilities for extrarenal excretion of the individual urinary constituents.

TABLE 2.—*Concentration of Substances by Kidney*

Substance	Concentration in Urine, Mg. per Cent	Concentration in Blood, Mg. per Cent	Number of Times Concentrated	Concentration in Blood in Renal Insufficiency
Urea	2,000	30	65	Increased
Uric acid	60	2	30	Increased
Creatinine	75	2	35	Increased
Indican	1	0.05	20	Increased
Phosphate	150	3	50	Increased
Sulphate	150	4	40	Increased
Potassium	150	20	7	Slightly increased
Chloride	500	350	1.5	Not increased
Sodium	350	300	1	Not increased
Calcium	15	10	1.5	Not increased
Magnesium	6	3	2	Not increased
Water	..	..	1	Not increased

3. Variations in the amounts of the individual urinary constituents brought to the kidney.

1. *Concentration Ratios.*—The work of the kidney consists almost entirely in a highly selective concentration and elimination of various constituents of the blood. If one compares the number of times the individual urinary constituents are concentrated by the kidney, it will be noted that there is a sharp difference between the substances which increase in concentration in the blood in uremia and those which do not (table 2).

From table 2 it is seen that those substances which accumulate in the blood in renal insufficiency are precisely the ones that are highly concentrated by the kidney, while the bodies with a normal level in the blood of the uremic patient are the ones whose average concentration in the urine is little or not at all greater than that in the blood. The urinary ammonium forms an obvious exception, being, in all probability, formed almost entirely by the kidney and not a simple excretion from the blood;

it is therefore omitted from table 2. Potassium, which undergoes only slight concentration, shows a comparatively small increase in the blood as a result of severe renal insufficiency.

The explanation of this parallelism between the degree of concentration of a substance by the kidney and its accumulation in the blood in renal failure would seem to be the following:

Let us consider those substances which are excreted almost entirely in the urine. The absolute amount of each of these substances eliminated in a twenty-four hour period is obviously proportional to its average concentration in the urine of that time. Also, in the presence of normal kidney function, the amount of each substance in the day's urine is equal to the amount that the tissues throw into the blood for excretion during that period. If, now, complete cessation of renal activity occurs, while ingestion and metabolism go on unchanged, the substances which should be excreted by the kidney will accumulate in the blood in amounts that are proportional, as just shown, to their respective average concentrations in the urine. And the number of times a substance increases in concentration in the blood will be proportional to this quantity (the average concentration in the urine) divided by the initial concentration in the blood. In other words, the normal value of the ratio average concentration in urine: concentration in blood is a measure of the number of times a substance will increase in concentration in the blood if renal insufficiency sets in, provided extrarenal factors remain unchanged. To illustrate: The concentration ratio for urea is $\frac{\text{2,000 mg. per hundred cubic centimeters}}{\text{30 mg. per hundred cubic centimeters}} = 65$ and for chloride $\frac{\text{500 mg. per hundred cubic centimeters}}{\text{350 mg. per hundred cubic centimeters}} = 1.5$. Therefore, if renal function is completely inhibited, under the ideal conditions of unchanged ingestion and metabolism, the concentration of urea will multiply in the blood $\frac{65}{1.5} = 43$ times as rapidly as will the concentration of chloride. And if it takes one day for the urea concentration of the blood to double, it would take forty-three days to double the chloride concentration.

Calculations such as the foregoing can be only rough approximations at the best, for they do not take into consideration the possibility that the distribution of different substances between blood and tissues may be differently affected by retention. But the foregoing considerations do serve to indicate why it is so much more difficult for renal insufficiency to raise the level in the blood of a substance like chloride, which is little concentrated by the kidney, than of the highly concentrated urea.

2. *Extrarenal Excretion.*—In studying the blood chemistry of renal insufficiency, it must be remembered that certain of the urinary constituents may also be excreted by channels other than the urine. Thus, under normal circumstances about 40 per cent of the total water excre-

tion is eliminated extrarenally.[16] Likewise, probably the greater part of the calcium and magnesium is eliminated through the bowel. From what we know of the factor of safety with which almost all of the bodily functions are endowed, it is obvious that in the case of these substances elimination will be completed by vicarious activity of the respective extrarenal organs of excretion despite complete cessation of activity of the kidney. The kidney can quickly eliminate a large quantity of water, but under ordinary circumstances where speedy elimination is not required, the lungs and skin can excrete the necessary amount of water. It is thus readily understandable why, despite numerous past assertions to the contrary, recent investigations[17] with more adequate methods have not revealed an increase in the blood volume in chronic renal insufficiency. In the case of other substances, however, such as the nitrogenous constituents of the urine and chloride, the proportion eliminated extrarenally is small and cannot be increased sufficiently to compensate for defective renal function. So in the case of these substances, extrarenal elimination will not suffice to prevent accumulation in the blood.

3. *Variations in Supply.*—Nor must we think of the urinary constituents solely from the point of view of excretion. Alterations in the source of supply must be considered. With the exception of potassium, all the substances in the group that increases in renal insufficiency are obligatory and products of the catabolism of tissue proteins, and while they may be diminished in amount by the elimination of protein from the diet, they continue to be produced in considerable quantity under all circumstances from the breakdown of tissue protein. On the other hand, the group of substances that do not increase in renal insufficiency can be caused almost to disappear from the urine by eliminating them from the dietary. So that from this standpoint there also is a significant difference between the two groups, in that by a suitable dietary we can almost remove the necessity for the excretion of the substances of the second group, but this is not feasible in the case of the protein derivatives. It is thus readily comprehensible why such substances as chloride do not show even a slight increase in the blood of patients with chronic uremia, but more often an actual decrease; it is because these patients have been kept on a salt-poor diet furnishing even less chloride than the severely injured kidney can excrete. Moreover, there is often a considerable loss of chloride by vomiting.

16. Roth, N.: Beiträge zum extrarenalen Wasserstoffweschsel bei Normalen und Nephritiden, Ztschr. f. klin. Med. **98**:305 (March) 1924.

17. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillmann, E. G.: Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, J. Exper. Med. **39**:921 (June) 1924. Brown, G. E., and Rowntree, L. G.: The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, Arch. Int. Med. **35**:129 (Jan.) 1925.

A special position is occupied by those urinary constituents (hippuric acid, ammonium) which are formed by the kidney itself. These, it would be expected, should not accumulate in the blood in renal insufficiency, and it has in fact been shown [18] that in uremia the ammonium content of the blood is normal and that of the urine diminished.

THE URINE IN IMPAIRED RENAL FUNCTION

It has long been known that when renal function is impaired the specific gravity of the urine is low and cannot be raised by any of the agencies, such as restriction of fluids, profuse sweating and cardiac failure, under the influence of which a normal kidney elaborates a highly concentrated urine. It was shown by von Koranyi [9] that the low specific gravity of the urine is due to a decrease in the total molecular concentration, for the depression of the freezing point is less than normal. As the freezing point and therefore the osmotic pressure of the urine in renal injury tend to remain constant near that of the blood serum, he termed the condition isosthenuria.

We have studied the concentrating power of the kidney, using the technic described below for the concentration test, and have found the characteristics of the urine in chronic impairment of renal function, as regards the specific gravity, urea, and chlorid concentrations, to be the following:

Specific Gravity.—As is well known, the maximum specific gravity of the urine falls progressively as the kidney fails and forms a measure of the functional capacity of that organ. (By maximum specific gravity is meant the highest specific gravity reached in the concentration test.) The lowest point to which the maximum specific gravity attainable by sufficiently prolonged deprivation of fluid falls is 1.010. We have reference, of course, only to nonedematous patients, for in the presence of resorbing edema it is often impossible to ascertain the maximum concentrating power of the kidney, owing to a constant supply of water from the edema fluid. Only in isolated instances have we been unable to attain a specific gravity of 1.010 by the thirst procedure, and in these the maximum was either 1.008 or 1.009.

We have not seen a single instance of true chronic uremia [19] in which the maximum specific gravity of the urine was not under 1.020.

18. Russell: Ammonia Content of the Blood in Nephritis, Biochem. J. **17**:72, 1923.

19. The term uremia is used, following Volhard,[8] for a group of symptoms resulting from retention of urinary constituents and therefore always found in association with renal insufficiency; these symptoms occur most typically in anuria due to mechanical obstruction. It will bear repetition that by no means all the nervous phenomena occurring in the course of Bright's disease are uremic in nature, but that convulsions, amaurosis, transient palsies, etc., may occur in the presence of intact renal function, being in some way correlated with the hypertension.

almost always under 1.015. In cases of uremia terminating chronic Bright's disease in which the highest specific gravity attainable was between 1.015 and 1.019, there was always evidence of marked myocardial insufficiency. In azotemic patients without well marked myocardial insufficiency, the maximum specific gravity was below 1.015, terminating in inability to concentrate above a specific gravity of 1.010. Recently, we were able to examine the last 50 cc. of urine eliminated by a patient dying of uremia without any evidence of myocardial insufficiency, i. e., a purely "renal" death, and found the specific gravity to be 1.010. Necropsy revealed a primary contracted kidney complicated by slight bilateral pyonephrosis. The wall of the left ventricle was greatly thickened, but there was no evidence of dilatation, the chamber of the left ventricle being very small. It would seem that maximal impairment of renal function (apart from total anuria) is characterized by inability of the kidney to elaborate a urine of concentration higher than that represented by a specific gravity of 1.010.

Urea.—The fact that patients whose renal function is defective have impaired concentrating power for urea has been used by Maclean [20] as the basis of his well known urea concentration test. Using the concentration test as described below, we have found that patients with maximal impairment of concentration, i. e., with a maximum specific gravity of 1.010, cannot elaborate urine containing more than 0.9 per cent of urea, and the maximum is usually much less. Under these conditions a normal kidney readily concentrates urea to over 2 per cent.

Chloride.—The maximum concentration of chloride in the urine of patients with impaired renal function is more difficult to ascertain than that of urea because of the frequent complication by myocardial insufficiency which, as is well known, greatly reduces the concentration of chloride in the urine, even though the kidney is normal. If the patient has been on a salt-poor diet for some time, it is difficult to find the maximal renal insufficiency (maximum specific gravity, 1.011), the the avidity of the tissues for salt. We have found that in instances of maximaly renal insufficiency (maximum specific gravity, 1.010), the highest concentration of chloride attainable is always low; the highest we found was 0.42 per cent (calculated as sodium chloride), and in many instances we were unable to obtain nearly so high a concentration. Under similar conditions the normal kidney produces urine containing over 1 per cent, often over 1.5 per cent sodium chloride. In accord with this, De Wesselow [21] has recently found that "the kidney in interstitial nephritis shows, when examined by a chloride concentration test, an

20. Maclean: Modern Methods in the Diagnosis and Treatment of Renal Disease, Ed. 2, Philadelphia, 1924, p. 59.

21. De Wesselow, O. L. V.: The Excretion of Chlorides by the Healthy and Diseased Kidney, Quart. J. Med. **19**:53 (Oct.) 1925.

inability to concentrate chlorides running parallel with the failure of the capacity to concentrate urea." Despite this impairment of the ability to concentrate chloride there is no chloride retention in chronic renal insufficiency for reasons given in the foregoing. But Veil [22] has shown that retention with a marked rise in the concentration of chloride in the blood may be produced in renal insufficiency by the ingestion of excessive amounts of chloride.

Studies on the concentration of calcium in the urine in impaired renal function have been carried out recently by Hetényi and Nógrádi.[23] They found that when renal function is impaired the ability of the kidney to concentrate calcium is greatly diminished. Nevertheless, in the case of calcium as in that of chloride, we have seen that there is no retention, for calcium is a substance that is normally but slightly concentrated by the kidney, and is also excreted by the intestine in probably even larger quantities than by the kidney.

CHLORIDE RETENTION

There are many instances of Bright's disease in which the outstanding clinical manifestation is edema. These are the cases that are generally known as the "chloride retaining" form, and it is widely believed that in these instances there is specific injury to the ability of the kidney to excrete sodium chloride. The explanation of the edema as due to impairment of the power of the kidney to excrete salt is largely based on the fact that the urine of such patients contains little sodium chloride, and that in certain edematous patients with Bright's disease—as in the classical case of Widal and Javal [6]—it is possible to increase or decrease the edema at will by feeding or restricting sodium chloride.

Glomerulonephritis may present for a long time the picture of isolated chloride retention, but this may at any time be complicated by the development of nitrogen retention, thus producing a "mixed" case. The classical picture of isolated chloride retention is seen in lipoid nephrosis. In these cases, anatomically characterized by purely degenerative lesions of the tubules of the kidney, there is no evidence of any injury to kidney function. The urine is of high specific gravity; the nonprotein nitrogen and chloride of the blood are not increased; the Ambard constant and urea concentration tests are normal, and dyes are excreted promptly. That the low concentration of sodium chloride in the urine in nephrosis is not due to a specific inability of the kidney to excrete salt is proved by the diuresis with a high concentration of sodium

22. Veil: Ueber die Bedeutung intermediaerer Veraenderungen im Chlorstoffwechsel beim Normalen und beim Nierenkranken, Biochem. Ztschr. **91**:299, 1918.

23. Hetényi, G., and von Nógrádi, S.: Ueber die Kalkausscheidung der gesunden und kranken Niere, Klin. Wchnschr. **4**:1308 (July 2) 1925.

chloride in the urine often initiated by Epstein's [24] treatment with high protein feeding and the administration of thyroid, measures that surely do not serve to improve the concentrating power of the kidney. That chloride retention in itself does not cause any considerable edema is proved by cases of mechanical anuria with high blood chloride concentration (described above) which do not present edema. The primary cause of the edema in Bright's disease has been shown by numerous researches in recent years to be extrarenal, in nephrosis being correlated with the low protein content of the blood (Epstein) and in nephritis possibly with changes in the capillary walls.

The low concentration of sodium chloride in the urine—sometimes there may be only mere traces present—is, I believe, explained by the fact that the concentration of sodium chloride is higher in the transudates than in the blood, which serves to reduce the concentration of sodium chloride in the blood to near the threshold value and thereby inhibits its excretion. In other words, the diminished excretion of chloride is not the cause of the edema but the result of it, and to consider edematous types of Bright's disease as examples of selective injury to one of the functions of the kidney (sodium chloride excretion) is erroneous. The "pure" picture of chloride retention is produced by the combination of an extrarenal cause for edema with intact kidney function, though of course impairment of renal function may also be present or supervene at any time, thereby producing a mixed case.

ANATOMIC BASIS AND NATURE OF IMPAIRMENT OF RENAL FUNCTION

It has been seen that when the kidney fails in chronic Bright's disease, this failure is always manifested in the same way, namely, by a lowering of the maximum concentrations of the individual urinary constituents. If the impairment of renal function progresses, the maximum specific gravity attainable falls further and further, till the most concentrated urine that the kidney can elaborate is that with a specific gravity of 1.010, which is approximately the specific gravity of deproteinated blood serum. It was also seen that in cases in which chloride alone is retained, the urine has a normal or high specific gravity and there is no impairment of renal function.

We have studied the blood and urine in uremia due, not to Bright's disease, but to the so-called surgical diseases of the kidney and urinary passages. The material studied comprised cases of uremia caused by:

Prostatic enlargement.
Paralysis of the bladder in tabes.
Polycystic kidneys.
Pyelonephrotic and tuberculous destruction of the renal parenchyma.

24. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167 (Feb.) 1922.

It was found that, apart from instances of total anuria (described above), the changes in the blood and urine are identical with those just described as occurring in the uremia of Bright's disease. Just as in Bright's disease, there is progressive diminution in the concentrating power of the kidney, ending in inability to elaborate a urine of specific gravity above 1.010, which is light in color and contains less than 0.9 per cent urea and 0.45 per cent sodium chloride. As long as water is in any way available, even by dehydrating the tissues, there is polyuria in an effort to compensate for the loss of concentrating power. In the blood, those substances, such as urea, which are highly concentrated by the kidney increase in amount while the chlorides are normal or even markedly diminished, except in total anuria as noted above, and there is acidosis, presumably largely from phosphate retention. The following are typical examples:

G. K. had bilateral polycystic kidneys. The systolic blood pressure was 210, diastolic 100. Concentration and dilution tests revealed a maximum specific gravity of 1.010 and a minimum of 1.008. The phenolsulphonphthalein output was less than 1 per cent. Blood analysis revealed: nonprotein nitrogen, 133.3; urea nitrogen, 113.4; uric acid, 4.5, and creatinine, 4 mg. per hundred cubic centimeters; plasma chlorides, 590 mg. of sodium chloride per hundred cubic centimeters, and carbon dioxide combining power, 26 per cent by volume.

A. L. had nephrolithiasis, bilateral ureteritis and pyelonephrosis. The maximum specific gravity was 1.010, and the phenolsulphonphthalein output almost 0. Blood analysis revealed: nonprotein nitrogen, 136.5; urea nitrogen, 75.6; uric acid, 5.2, and creatinine, 3.6 mg. per hundred cubic centimeters; plasma chlorides, 420 mg. per hundred cubic centimeters (as sodium chloride). The patient died from uremia.

In prostatic hypertrophy the concentrating power often returns so rapidly after the obstruction has been relieved that it seems probable that the impairment of renal function is not due to organic changes in the kidneys. In a tabetic patient with paralysis of the bladder and the typical blood and urine changes of renal insufficiency (maximum specific gravity, 1.012), renal function was quickly restored by the insertion of an indwelling catheter, but concentrating power was again lost after the catheter had been removed for some time.

The foregoing would seem to indicate that no matter in which way the kidney is diffusely injured—whether by inflammatory or arteriosclerotic changes, by cystic transformation and compression in polycystic kidneys, or by increase of urinary pressure starting from obstruction of the urinary passages—impairment of renal function is always manifested in the same way; namely, by a lowering of the maximum concentration in which the individual urinary constituents can be eliminated, thereby producing the typical "chemical picture" in the blood and urine described above. So far as we know, there is only one variety of impaired renal function—that in which all the excretory functions are injured—and

impairment of renal function may vary quantitatively but not qualitatively.

It is therefore justifiable to speak of impaired renal function as renal hypofunction. It is important to realize clearly the difference between renal hypofunction and renal insufficiency. Renal insufficiency is the analog of cardiac insufficiency and means that because of defective kidney function the necessary quantity of waste products is not being excreted. The criterion of renal insufficiency is the accumulation of excretory products in the organism, just as the criterion of cardiac insufficiency is the presence of such conditions as dyspnea and edema. On the other hand, renal hypofunction means only that renal function is impaired, though excretion may be completely performed by a compensatory mechanism (polyuria) and the organism as a whole does not suffer. The criterion of renal hypofunction is loss of concentrating power. The concept of renal hypofunction is broader than, and inclusive of, the concept of renal insufficiency.

In this connection, it may be recalled that Ambard [25] has claimed that the maximum concentrations of the various urinary constituents are isotonic with one another, and that a reduction in one is accompanied by a proportional reduction in the others. Whether or not this generalization has exact quantitative validity, we are not in a position to judge.

It is difficult to explain why such anatomically variegated injuries to the excretory functions of the kidney are all manifested by a decrease in the concentrating power, the extreme of which is in all cases at the same concentration (maximum specific gravity, 1.010). The old experiments of Bradford [26] showed that ablation of the greater portion of the renal parenchyma causes a polyuria with low specific gravity like that of impaired renal function in man. Richards [27] has demonstrated that only a fraction of the total number of glomeruli function at the same time. And Rabinowitch [28] has calculated that it takes less work to eliminate a gram of any substance in dilute solution than in a more concentrated solution. On the basis of these findings, a teleologic interpretation of the low concentration of the urine occurring in widespread renal injury may be advanced. It may be considered that the remaining kidney elements, having less rest, always elaborate urine in the most economical manner as regards actual work performed, which is in dilute

25. Ambard: Physiologie normale et pathologique des reins, Ed. 2, Paris, 1920, pp. 185-188.

26. Bradford: The Influence of the Kidney on Metabolism, Proc. Roy. Soc. London **51**:25, 1892.

27. Richards, A. M.: Kidney Function, Am. J. M. Sc. **163**:1 (Jan.) 1922.

28. Rabinowitch, I. M.: A Quantitative Index of Kidney Function; Thermodynamic Considerations in Estimation of Renal Efficiency, Arch. Int. Med. **34**:365 (Sept.) 1924.

solution. But teleologic interpretations in medicine are always risky. Nevertheless, it seems significant that in the severest impairment of renal function, the maximum specific gravity of the urine does not fall below 1.010, at which level the osmotic pressure of the urine approximates that of the blood. However, even in urine of specific gravity 1.010, the maximum urea concentration is still many times that of the blood, while the maximum chloride concentration is less than that of the blood. Such differences are difficult to interpret.

COMPENSATION AND DECOMPENSATION IN RENAL HYPOFUNCTION

Since the functionally impaired kidney is unable to elaborate a concentrated urine, it can meet an increased demand only by increasing the volume of the urine, and as the injury to the kidney progresses polyuria becomes necessary to eliminate the waste products even from a basal diet. The polyuria of renal hypofunction is a true compensatory mechanism comparable to the cardiac hypertrophy following a valvular lesion. The stage in which there is impairment of the concentrating power of the kidney and yet excretion is completely performed through the mechanism of polyuria may be termed the stage of compensated renal hypofunction. Such cases may go into the stage of decompensated renal hypofunction, marked by retention of urinary constituents in the blood, if the volume of urine diminishes. This reduction in the polyuria may be due to myocardial weakness resulting from the hypertension, or to injury to so large a proportion of the glomeruli that the necessary amount of water cannot be eliminated. I have several times seen the onset of decompensation with uremia accompany the oliguria of an intercurrent febrile complication; here, presumably, the increased metabolism with resultant rise in the catabolites to be eliminated also played a part.

The concepts of compensated and decompensated renal hypofunction are of fundamental significance for the interpretation of tests of renal function.

Compensated Renal Hypofunction.—In this stage the concentrating power of the kidney is impaired, but this is compensated for by an increase in the volume of urine, so that there is no retention and the blood chemistry is normal. In fully compensated renal hypofunction the functional tests that are based on measuring the quantity of some substance eliminated in a given time (e. g., the phenolsulphonphthalein test) give a normal result if sufficient water is available; the test substance is excreted by means of a polyuria in the usual time though in lesser concentration. In order to detect compensated renal hypofunction, it is necessary to determine the maximum concentration of the urine. In the calculation of the Ambard constant, the concentration of

urea in the urine is considered, but this concentration is a random one and not necessarily the maximum. Moreover, Maclean [20] has pointed out that the arrangement of the formula is such that variations in the urinary concentration play only a relatively small rôle in comparison to changes in the blood urea. Maclean's urea concentration test reveals admirably the presence of renal hypofunction, but it involves a chemical determination in the urine. From the foregoing it is seen that we can dispense with any chemical determination, for renal hypofunction will be revealed by an abnormally low specific gravity of the urine under circumstances in which the functionally intact kidney would elaborate a urine of high specific gravity. These principles are applied in the concentration and dilution tests of Volhard,[29] which we have found to be the best means of detecting compensated renal hypofunction.

Volhard's technic, which we followed originally, consists in having the patient empty his bladder on rising in the morning and then drinking 1,500 cc. of water (we have found 1,200 cc. ample) within a half-hour. For the rest of the day the patient takes only dry food. The patient voids every hour in the morning and every two hours in the afternoon and the volume and specific gravity of the individual specimens are recorded. The normal patient voids the ingested water within four hours and his urine attains a specific gravity of from 1.028 to 1.034 late in the afternoon or early evening.

We have found that attempts to carry out both the concentration and dilution tests in the same day often lead to failure to attain the maximum specific gravity of which the kidney is capable because of the delayed excretion of the ingested water. This prolongation of water elimination may be due to myocardial insufficiency or be a manifestation of severe renal injury, which may protract the excretion of the water to twenty-four or more hours. To obviate this we perform the concentration test alone, in the following simple way:

The patient has his customary supper and then takes no fluids till four hours after waking the next morning. On waking, he empties his bladder; this urine is discarded. He voids hourly for three hours and the specific gravity and volume of each specimen is recorded. Should he be unable to pass urine each hour, one is omitted, so that there are only two specimens. It is best that the patient remain in bed during these hours. The highest specific gravity of the three specimens is considered as representing his maximum concentrating capacity. In health the specific gravity reaches from 1.026 to 1.034, usually about 1.030. We have not seen true uremia in any case in which the maximum specific gravity reached 1.020 or over. A maximum specific gravity under 1.020 indicates impaired renal function. In the severest

29. Volhard (Footnote 5, p. 1198).

cases the patient is unable to concentrate above 1.010. Small amounts of albumin do not notably affect the result. In evaluating the results one must always be sure that edema or a serous effusion is not being evacuated, for this may simulate inability to concentrate.

Decompensated Renal Hypofunction.—In the decompensated stage of renal hypofunction, the loss of concentrating power is not balanced by an increased urinary volume, and retention of the substances that are normally highly concentrated by the kidneys occurs. To demonstrate the existence of the decompensated stage, therefore, it is necessary to find retention of urinary constituents in the blood, though the presence of renal decompensation may be surmised from the combination of a low maximal specific gravity of the urine with oliguria or a very low phenolsulphonphthalein output. Either the urea or the nonprotein nitrogen concentration of the blood may be used as an indicator of the onset of decompensation. Theoretically, the determination of urea is preferable to that of nonprotein nitrogen because the urea concentration in the blood is approximately equal to that in the tissues,[30] even in the most marked retention,[31] while the nonprotein nitrogen content of the tissues is much greater than that of the blood. We have not found that uric acid and creatinine determinations, which are much more liable to error than the estimation of urea, yield any diagnostic or prognostic information not afforded by the urea concentration.

PRERENAL DEVIATION

When renal function is impaired the power of the kidney to eliminate water, as judged by the Volhard water test, often remains surprisingly good for a considerable time, but ultimately becomes impaired, and in addition to inability to concentrate the patient can no longer elaborate a very dilute urine. In such cases the defective water elimination, if not cardiac, is merely part of the impaired renal function which affects the excretion of all the urinary constituents.

Much more common than defective water excretion as a manifestation of impaired renal function is failure of water excretion due to extrarenal causes. Such cases are recognized by the unimpaired concentrating power of the kidney revealed by the high specific gravity of the urine. As stated above, there is little sodium chloride in the urine, but this in itself does not suffice to depress the specific gravity markedly. If such a patient drinks 1,500 cc. of water only a small portion is eliminated within four hours. The rest "leaks away" into the tissues, lowering the water content of the blood close to the water threshold; this prevents

30. Marshall and Davis: Urea: Its Distribution in and Elimination from the Body, J. Biol. Chem. **18**:53, 1914.

31. Weiss and Vaughn: Chronic Nephritis with an Unusual Degree of Nitrogen Retention, J. Lab. & Clin. Med. **7**:229, 1921.

the copious diuresis that normally follows the drinking of so much water. This abstraction of fluid from the blood may aptly be termed prerenal deviation. It is encountered in such varied conditions as nephrosis, certain cases of glomerulonephritis, myocardial failure, high intestinal obstruction and profuse diarrhea. The urine in prerenal deviation is reduced in volume, of high specific gravity, with a high concentration of urea but a low concentration of chloride. The blood urea may rise to great heights if there is marked oliguria while the chloride content may be very low if the fluid lost contains much chloride. The relations between compensated and decompensated renal hypofunction and prerenal deviation are summarized in table 3.

TABLE 3.—*Relation of Compensated and Decompensated Renal Hypofunction and Prerenal Deviation*

	Concentrating Power	Diluting Power	Blood Urea
Compensated renal hypofunction.....	Impaired	Normal	Normal
Decompensated renal hypofunction (renal insufficiency)	Impaired	Normal or impaired	Elevated
Prerenal deviation	Normal	Impaired	Normal or elevated

SUMMARY

1. Impairment of renal function involves all the excretory functions of the kidney.

2. No matter what the anatomic substratum—arteriosclerotic or inflammatory change, polycystic transformation or prostatic obstruction—impairment of renal function is always manifested in the same way, namely, by a lowering of the maximum concentration in which each of the individual urinary constituents can be excreted.

3. As impairment of renal function progresses, the maximum specific gravity attainable falls correspondingly. But no matter how severe the injury to renal function, the maximum specific gravity attainble does not fall below 1.010.

4. When selective retention occurs in Bright's disease, it is not due to inability of the kidney to excrete the retained substance but to the intervention of an extrarenal factor.

5. The primary criterion whether or not a substance rises in concentration in the blood as a result of renal insufficiency is the normal value of the ratio $\frac{\text{average concentration in urine}}{\text{concentration in blood}}$ for that substance. If this ratio is high (e. g., urea) the substance will accumulate in the blood in renal insufficiency, while if the ratio is low (e. g., chloride) it will not.

6. Fully compensated renal hypofunction is revealed only by a lowered maximum concentration of the urine, for the detection of which a modification of Volhard's specific gravity test is used.

Book Reviews

GASTRIC FUNCTION IN HEALTH AND DISEASE. By JOHN A. RYLE, M.D., F.R.C.P., Assistant Physician and Lecturer on Medical Pathology, Guy's Hospital, London. Pp. 152. Oxford Medical Publications, 1926.

In this short monograph the author first considers the sensory, motor and secretory functions of the stomach in health. The normal gastric sensations are described and explained. The variations in gastric secretion are considered as expressions of variations in tonus, peristalsis and motility. In health they may range from complete "achlorhydria" to extreme "hyperchlorhydria." A correlation is found between the physical type of the subject and the type of gastric response, both motor and secretory. An entire chapter is devoted to the function and control of the pylorus and to the control of gastric acidity. In gastric disease, the painful sensations are ascribed to an increase of tension in the muscle fiber and the suggestion is made that nausea and anorexia are associated with abnormal relaxation. A classification of the common dyspepsias is given and discussed. One chapter is devoted to gastrojejunostomy and its sequelae.

The fractional test meal is accorded more value than seems justifiable on the basis of the data given. The author endeavors to show that all gastric distress is due to variations in the tension of the gastric musculature, and that such distress may be induced reflexly by extragastric lesions as well as by local gastric disease. The evidence presented is entirely insufficient and the view taken serves only to make the subject of abdominal symptomatology more difficult. The portion devoted to the dyspepsias has little interest. In the chapter on gastrojejunostomy, the conclusion is reached that "the most important contraindications to gastrojejunostomy are a short history, a well marked hypertonus, a high abrupt curve of acidity, and rapid emptying. The most reasonable indications for operation apart from obvious stenosis are a long history, a subnormal tonus, a slowly climbing curve, and slow emptying."

On the whole, the book is not very practical; it adds further confusion to the subject of gastro-intestinal physiology and symptomatology.

IMMUNOCHEMICAL STUDIES. By CARL H. BROWNING, WITH M. KOSAKAI, T. J. MACKIE, T. TANIGUCHI, G. H. WILSON, N. YOSHINARE. Pp. 239. Price, $4.50. New York: William Wood & Co., 1925.

It would be refreshing to read a treatise on the topic designated by the title in which the discussions are made in a relatively simple and clear manner, and without reference to the befuddling terminology existent in the field of immunology during the last twenty years. Such desired clarity is not contained in this volume; in fact, a survey of the literature references quoted demonstrates that most of the text could have been written as well ten years or more ago as in 1925. If an attempt was made to add new facts or ideas in the field of immunology the effort was futile.

SCOLIOSIS. By SAMUEL KLEINBERG. Pp. 291. Price, $6. New York: Paul B. Hoeber.

This is an excellent and comprehensive treatise on scoliosis. It places special emphasis on the abandonment in the severe cases of the time honored exercises, braces and casts. The correction of the deformity, so far as possible, is accomplished by plaster jackets applied by the Abbott method or by the Kleinberg method, followed by his ingenious and satisfactory brace. When the maximum correction has been attained, a fusion operation, which is in

effect a combination of the Hibbs operation and a bone splint, is then performed. It is somewhat surprising to note Kleinberg's advocacy of beef bone splints, in view of the fact that most operators have abandoned the use of beef bone except in the form of screws or intramedullary pegs. The book is a definite step forward in the elimination of much that is, or should be, obsolete in the treatment of this distressing deformity. The views on operative treatment, while somewhat advanced, will undoubtedly find wide acceptance among the modern practitioners of orthopedic surgery.

NEPHRITIS. By DR. HERMAN ELWYN. Price, $5. New York: Macmillan Company.

This book is largely a compilation, but in the assembling of facts and theories Dr. Elwyn has shown an unusual amount of wisdom. He has exercised editorial discretion as to what to include and what to omit. The result is a well considered, comprehensive résumé of the essentials of present day knowledge of nephritis. The author has injected his own personality into the book. His views are never in doubt, but they are not offensively obtruded. Moreover, they are clearly the result of wide reading, close observation at the bedside, and intimate familiarity with the laboratory. But all the knowledge contained in the volume, and all the wisdom manifested in working over that knowledge might have been largely wasted had there been lacking skill in presentation. Fortunately there is no such lack. The author has the gift of style. He knows how to condense, how to write simply yet with scientific accuracy, how to present a subject in an orderly manner. He writes attractively, forcefully and clearly.

The work includes a brief review of the anatomy and physiology of the kidney, a discussion of renal insufficiency, hypertension and uremia. The various classifications of nephritis are reviewed and that of Volhard and Fahr rather closely followed. The etiologic, pathologic and clinical features of the various types of nephritis are then considered with sufficient but not bewildering detail, due to attention being given to treatment.

The book is written from the modern point of view of nephritis. The practitioner who has had difficulty in keeping up with the recent advances and who may be bewildered by references in the literature to arteriolosclerosis, nephrosis, Mosenthal meals, nonprotein nitrogen of the blood, etc., will find the book helpful. To him as to the medical student it may be heartily recommended.

A MANUAL OF CLINICAL LABORATORY METHODS. By C. L. CUMMER, PH.B., M.D. Second edition, revised. Pp. 547; 181 illustrations. Price, $6.50. Philadelphia: Lea and Febiger, 1926.

The first edition of this manual contained concise instructions for making any of the usual simple and the more complicated clinical laboratory examinations. To these are added in this new edition certain revisions, notably in the chapter dealing with the Wassermann reaction. Other changes are made in the directions for the chemical examinations of the blood. A section on cutaneous reactions and a chapter on basal metabolism are new features.

As a text for medical students and a guide for physicians and laboratory technicians, this book is recommended without reserve and is adequate in every respect.

PSYCHOANALYSIS AND BEYOND PSYCHOANALYSIS. By LEONARD L. LANDIS, M.D., 140 East Twenty-Second Street, New York.

There is no merit in this book either from the standpoint of the medical man or of the lay public. It is stamped by the author's picture and by the introduction; the two, fortunately coming at the beginning of the book, should be words to the wise. There are statements made throughout the book that either fail in sense or are unfortunate interpretations of the work of other men.

DEVELOPMENT OF OUR KNOWLEDGE OF TUBERCULOSIS. By LAWRENCE F. FLICK, M.D., LL.D., Cofounder of the Rush Hospital for Diseases of the Chest; Cofounder of the Henry Phipps Institute. Pp. 783. Price, $7.50. Lancaster, Pa.: Press of Wickersham Printing Company, 1925.

This is a well written, erudite exposition of the history of the steps in our knowledge of tuberculosis and its problems from early times to the beginning of this century. Some evidence is produced to the effect that references to this disease were made in the Code of Hammurabi, written 2,250 years before the Christian era, and later in the Hearst medical papyrus, dating back to about the ninth year of Amenophis I, about 2,000 years before the Christian era. These references are implied but the story becomes more complete and more definite in the Hippocratic writings. From this point on the sequence is unbroken and each step is carefully considered. It represents an exhaustive study of the literature, both ancient and modern; it shows that what has been learned has been the result of observation and study by many students from generation to generation—a countless number of workers and contributors who have added to, confirmed or corrected the theories and facts of those who have preceded them. Our knowledge of tuberculosis is the sum of centuries of individual effort and team work.

This volume will be of exceptional interest to phthisiologists and to medical historians but should also be of value and inspiration to all students and practitioners of medicine.

LA ARTERITIS PULMONAR, CARDIACOS NEGROS. By F. C. ARRILLAGA. Buenos Aires: Pedro Garcia.

This is an excellent monograph of 375 pages. It is profusely illustrated with photomicrographs, roentgenograms and drawings, several of which are in color. It represents a study of twenty-two cases of so-called "black cardiacs." Arrillaga's work puts this subject on a firm basis as a definite clinical entity. The patients are mostly old cardiac patients with histories of chronic arterial disease. They generally come to the hospital with a decompensation. Mitral stenosis occupies a prominent place in the etiology, being present in about one third of the cases. The clinical picture is most striking. In addition to the general cyanosis there is an extreme lividity of the hands, feet and head, the latter being a dark blue or even black. Dyspnea, tachycardia, cough and expectoration are marked. The urine is generally full of albumin. The blood picture is striking. The leukocyte count is normal in number and kind. There is, however, in every case a marked polycythemia, the red cells varying between five and a half and nine million. The clinical course is rapidly progressive and death usually ensues in a few months.

A complete study of the necropsy material on these cases has yielded definite results. There is an inflammation and intimal thickening of the pulmonary arteries. Aneurysm is common but the disease is most marked in the smaller branches in which there are invariably advanced stages of obliterating endarteritis. These are constant findings and are all beautifully illustrated in the monograph.

On the whole the author is to be congratulated on a brilliant piece of work.